

Introducing covalent warheads on spirocyclic sp^2 - sp^3 fragments by innate C-H functionalization

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General Methods

All reactions were carried out in round-bottom flasks or microwave tubes under a positive flow of nitrogen, unless otherwise stated. Commercially available reagents and solvents were used without further purification, except trifluorotoluene, which was distilled over P_2O_5 before use. They were supplied by Astatech, Merck, Combi-Blocks or SpiroChem and were of technical grade. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin-layer chromatography using Biotage KP-NH TLC Glass plates and visualized by fluorescence under UV light or by development with an aqueous $KMnO_4$ solution with gentle heating. Medium-Pressure Liquid Chromatography (MPLC) purifications of crude residues were performed on a Biotage Isolera IV System with Agela technologies pre-packed silica gel. Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure. Purified compounds were further dried under high vacuum (with a lyophilizer after reverse-phase). Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on a Bruker Ultrashield at 300 or 400 MHz (1H), 75 or 101 MHz (^{13}C), and 376 MHz (^{19}F) at 298K in the indicated deuterated solvent, unless otherwise stated. Chemical shifts are reported in ppm with the solvent resonance as the internal standard relative to, $CDCl_3$ ($\delta = 7.26$ for 1H , $\delta = 77.16$ for ^{13}C) and $MeOD-d_4$ ($\delta = 3.31$ for 1H , $\delta = 49.00$ for ^{13}C). All ^{13}C spectra were measured with complete proton decoupling. Data are reported as follows : s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, qt = quartet of triplets, qd = quartet of doublets, dd = doublet of doublets, ddd = doublet of doublets of doublets, ddt = doublet of doublet of triplets, dtt = doublet of triplet of triplet, dt = doublet of triplets, tdt = triplet of doublets of triplets, qdd = quartet of doublets of doublets, coupling constants J in Hz. Low resolution mass spectra by ESI-MS were recorded on Shimadzu LCMS-2020, coupled with Shimadzu LC-2040C Plus from the analytical service of SpiroChem. Masses on TLC were checked with the TLC-MS device from Advion using the Low Fragmentation and Low Temperature mode. High resolution mass spectrometry was performed by electrospray ionization-time of flight (ESI-TOF) using a standard deviation of 0.500 ppm on a Bruker Daltonics maXis. Physical-chemical properties were measured in the following way.

Sirius T3 is an automated instrument that allows the screening of compounds and the preparation of detailed physical chemical profiles. The device consists of a pH-meter electrode, a robot that prepares the solutions needed to perform the measurements, and a UVVIS spectrophotometer. If basic titration is needed, basic titration will be performed with

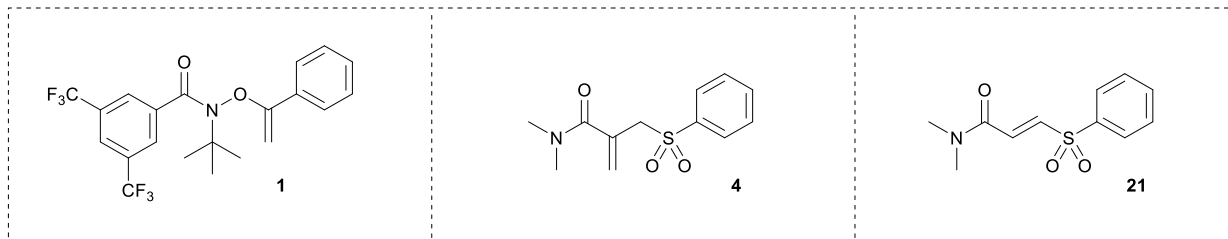
a 0.1M KOH buffer. If acidic titration is needed, this titration will be performed with a 0.1M HCl buffer. To obtain the pKa value of our molecules, a pH-metric titration experiment was carried out. Potentiometric measurement was done from pH 2 to pH 12 by adding 0.5M KCl solution. Measurement point was done every 0.2 pH value. After each addition, the sample is stirred for 60 seconds, and the pH value is then collected. The titration experiment was done 3 times. The given value is an average value of the 3 measurements. Log P was determined potentiometrically by using the "Shake flask" method, which consists of dissolving part of the solute in question in a volume of octanol and water, then performing pH titration. LogD was determined as the value of log P at a pH where the molecule was completely not ionised. Solubility measurements were performed using the CheqSol method developed by Pion. As in most cases, compounds are more soluble at pH where they ionized, the analyte was solubilized in acidic water, then pH-titration was performed, measuring the UV-Vis spectrum after each addition. The precipitation point was detected from the reduction of the light transmission during UV-VIS measurement, or manually when not obvious. The pH-titration was repeated several times around the precipitation point to determine the solubility value by averaging.

Abbreviations

HAT = hydrogen atom transfer; Bz = benzoyl-; Cbz = carbobenzyloxy-; Boc = *tert*-butyloxycarbonyl-; TFA = trifluoroacetyl-; DMF = *N,N*-dimethylformamide; HATU = hexafluorophosphate azabenzotriazole tetramethyl uronium.

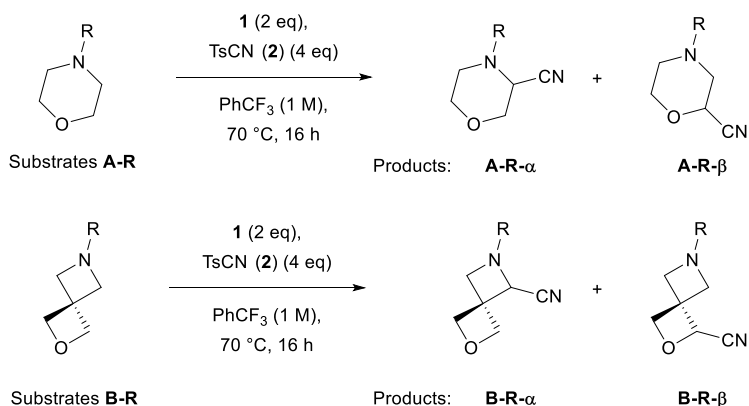
Experimental Procedures and Characterization Data

Reactants synthesis



HAT reagent **1**¹, allylic sulfone **4**², and vinyl sulfone **21**³ were synthesized according to literature reported procedures.

Preliminary results

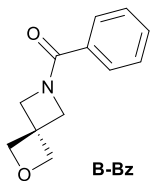


Substrate	Bz	Cbz	Boc	TFA	HetAr
A	n.r.	n.r.	40% α	n.r.	35% α
B	44% (1:1 α:β)	8% α	40% α	34% β	63% α

HetAr = 4-(2-chloropyrimidinyl)-

The reactions were run following previously reported conditions.¹ Substrates **A** and related products were synthesized according to reported procedures and matched characterization data.^{4,5} For **B-HetAr** (**3**) see “substrates synthesis” section. For **B-HetAr-α** (**3a**) see “HAT cyanation” section.

Note: Since the sole purpose of this preliminary stage was to explore reactivity, the cyanated products were identified with ^1H NMR and HRMS, without full characterization.



Compound B-Bz.

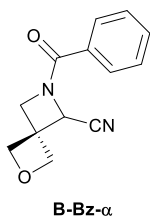
A suspension of 2-oxa-6-azaspiro[3.3]heptane hemioxalate (100 mg, 0.35 mmol, 1 eq) in DCM (3.47 mL, 0.1 M) was cooled to 0 °C. Triethylamine (211 mg, 290 μL , 2.08 mmol, 6 eq) and benzoyl chloride (195 mg, 161 μL , 1.39 mmol, 4 eq) were added dropwise. The mixture was allowed to warm to room temperature over 16 h, and then it was quenched with the addition of sodium bicarbonate (sat. aq. sol., 2 mL). The organic phase was separated, and the water phase was extracted with DCM (3 x 1 mL). The collected organic phases were washed with sodium chloride (sat. aq. sol., 5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (30% to 100% ethyl acetate), affording the desired product (121 mg, 0.60 mmol, 86% yield) as an amorphous white solid.

R_f 0.12 (*c*-hexane:EtOAc = 1:2, UV, KMnO_4).

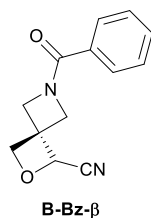
^1H NMR (400 MHz, CDCl_3) δ 7.67 – 7.57 (m, 2H), 7.51 – 7.37 (m, 5H), 4.81 (s, 4H), 4.39 (s, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 170.6, 132.9, 131.4, 128.6, 128.0, 81.0, 63.1, 58.4, 38.5. (Note: The carbons next to the nitrogen at 63.1 and 58.4 ppm split and are weak due to rotamerism).

HRMS (ESI-TOF, *m/z*) calcd. for $\text{C}_{12}\text{H}_{14}\text{NO}_2$ $[\text{M}+\text{H}]^+$ calc.: 204.1019; found: 204.1022.



B-Bz- α



B-Bz- β

Compound B-Bz- α and B-Bz- β .

Prepared using **B-Bz** (41 mg, 0.20 mmol, 1 eq), HAT reagent **1** (170 mg, 0.40 mmol, 2 eq), and TsCN (140 mg, 0.80 mmol, 4 eq) in PhCF_3 (200 μL , 1 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The two products were independently isolated as amorphous white solids (**B-Bz- α** : 10 mg, 0.04 mmol, 22% yield; **B-Bz- β** : 10 mg, 0.04 mmol, 22% yield), alongside recovered starting material (19 mg, 0.09 mmol, 47% yield).

B-Bz- α :

R_f 0.28 (*c*-hexane:EtOAc = 1:2, UV, KMnO_4).

^1H NMR (400 MHz, CDCl_3) δ 7.68 – 7.61 (m, 2H), 7.58 – 7.50 (m, 1H), 7.45 (t, J = 7.5 Hz, 2H), 5.14 (d, J = 7.9 Hz, 2H), 4.96 – 4.72 (m, 3H), 4.55 (d, J = 9.5 Hz, 1H), 4.38 (d, J = 9.4 Hz, 1H).

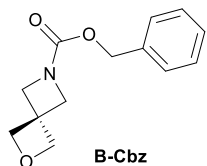
HRMS (ESI-TOF, m/z) calcd. for C₁₃H₁₂N₂NaO₂ [M+Na]⁺ calc.: 251.0791; found: 251.0787.

B-Bz-β:

R_f 0.23 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 7.66 – 7.58 (m, 2H), 7.55 – 7.48 (m, 1H), 7.44 (dd, *J* = 8.2, 6.6 Hz, 2H), 5.36 (br s, 1H), 4.92 (br s, 1H), 4.83 (br s, 1H), 4.69 (br s, 1H), 4.44 (br s, 3H).

HRMS (ESI-TOF, m/z) calcd. for C₁₃H₁₃N₂O₂ [M+H]⁺ calc.: 229.0972; found: 229.0967.



Compound B-Cbz.

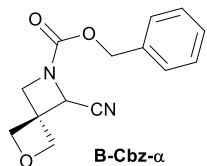
A suspension of 2-oxa-6-azaspiro[3.3]heptane hemioxalate (100 mg, 0.35 mmol, 1 eq) in DCM (3.47 mL, 0.1 M) was cooled to 0 °C. Triethylamine (211 mg, 290 μL, 2.08 mmol, 6 eq) and Cbz-OSu (190 mg, 0.76 mmol, 2.2 eq) were added in one portion. The mixture was allowed to warm to room temperature over 16 h, and then it was quenched with the addition of sodium bicarbonate (sat. aq. sol., 2 mL). The organic phase was separated, and the water phase was extracted with DCM (3 x 1 mL). The collected organic phases were washed with sodium chloride (sat. aq. sol., 5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 80% ethyl acetate), affording the desired product (141 mg, 0.60 mmol, 87% yield) as a colorless oil.

R_f 0.51 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.28 (m, 5H), 5.08 (s, 2H), 4.76 (s, 4H), 4.16 (s, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 156.3, 136.6, 128.6, 128.3, 128.2, 81.0, 67.0, 59.2 (x2), 38.4.

HRMS (ESI-TOF, m/z) calcd. for C₁₃H₁₅NNaO₃ [M+Na]⁺ calc.: 256.0944; found: 256.0943.



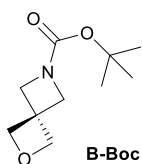
Compound B-Cbz-α.

Prepared using **B-Cbz** (47 mg, 0.20 mmol, 1 eq), HAT reagent **1** (170 mg, 0.40 mmol, 2 eq), and TsCN (140 mg, 0.80 mmol, 4 eq) in PhCF₃ (200 μL, 1 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 80% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). A colorless oil (5 mg) was isolated, containing a mixture of desired product (16 μmol, 8% yield) and recovered starting material (3 μmol, 2% yield).

R_f 0.56 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

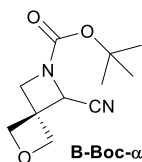
¹H NMR (400 MHz, CDCl₃) δ 7.54 – 7.41 (m, 1H), 7.35 (m, 4H), 5.15 (s, 2H), 5.07 (d, *J* = 8.2 Hz, 1H), 4.91 (s, 1H), 4.83 – 4.78 (m, 1H), 4.27 – 4.17 (m, 2H).

HRMS (ESI-TOF, m/z) calcd. for $C_{14}H_{14}N_2NaO_3$ $[M+Na]^+$ calc.: 281.0897; found: 281.0893.



Compound B-Boc.

The compound was synthesized following a reported procedure. The characterization data was consistent with the one in the literature.⁶



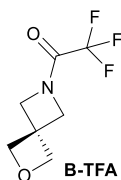
Compound B-Boc-α.

Prepared using **B-Boc** (20 mg, 0.10 mmol, 1 eq), HAT reagent **1** (86 mg, 0.20 mmol, 2 eq), and TsCN (72 mg, 0.40 mmol, 4 eq) in $PhCF_3$ (100 μ L, 1 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 80% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The product was isolated as a white amorphous solid (9 mg, 0.04 mmol, 40% yield).

R_f 0.35 (*c*-hexane:EtOAc = 3:1, $KMnO_4$).

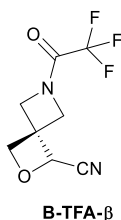
¹H NMR (400 MHz, $CDCl_3$) δ 5.06 (d, J = 7.8 Hz, 1H), 4.86 – 4.73 (m, 4H), 4.18 – 4.05 (m, 3H), 1.46 (s, 9H), 1.42 (s, 2H). (*Note: The compound presents rotamerism*).

HRMS (ESI-TOF, m/z) calcd. for $C_{11}H_{16}N_2NaO_3$ $[M+Na]^+$ calc.: 247.1053; found: 247.1052.



Compound B-TFA.

The compound was synthesized following a reported procedure. The characterization data was consistent with the one in the literature.⁷



Compound B-TFA-β.

Prepared using **B-TFA** (39 mg, 0.20 mmol, 1 eq), HAT reagent **1** (170 mg, 0.40 mmol, 2 eq), and TsCN (140 mg, 0.80 mmol, 4 eq) in $PhCF_3$ (200 μ L, 1 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The product was isolated as a white amorphous solid (15 mg, 0.07 mmol, 34% yield), alongside recovered starting material (23 mg, 0.12 mmol, 59% yield).

R_f 0.47 (*c*-hexane:EtOAc = 1:2, $KMnO_4$).

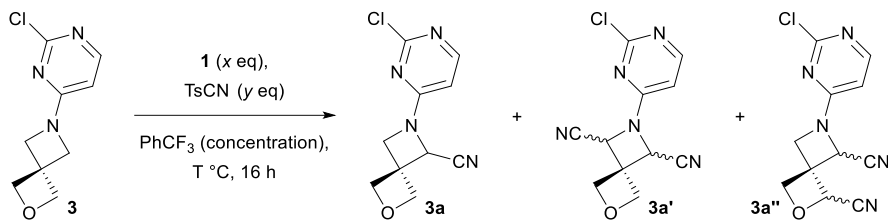
¹H NMR (400 MHz, $CDCl_3$) δ 5.37 (d, J = 4.4 Hz, 1H), 4.94 (dd, J = 7.3, 5.6 Hz, 1H), 4.87 – 4.80 (m, 2H), 4.70 – 4.54 (m, 2H), 4.44 – 4.32 (m, 1H). (*Note: The compound presents rotamerism*).

¹⁹F NMR (377 MHz, $CDCl_3$) δ -72.74, -72.75.

HRMS (ESI-TOF, m/z) calcd. for $C_8H_7F_3N_2NaO_2$ $[M+Na]^+$ calc.: 243.0352; found: 243.0350.

Optimization tables

HAT cyanation

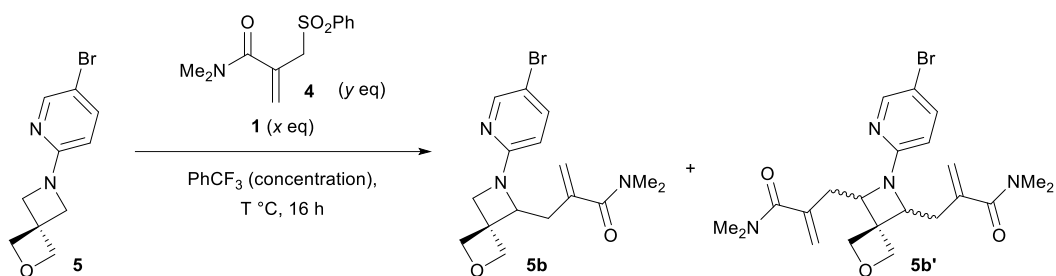


Entry	x	y	Concentration (M)	T (°C)	Yield (3:3a:3a'+3a''+3a''') %
1	2	4	1	70	0:63:36
2	2	4	0.75	70	0:63:36
3	1.5	4	0.75	70	10:64:10
4	1.5	2	0.75	70	20:68:10
5^a	2	4	0.75	70	30:52:0
6	2	4	0.75	90	0:51:25
7	2	6	0.75	70	0:63:36
8	3	4	0.75	70	0:40:50
9	3	6	0.75	70	0:40:55
10	4	6	0.75	70	0:40:46

a = non-distilled trifluorotoluene was used.

Note: the double-derivatized products were afforded as complex mixtures of regio- and diastereo-isomers.

HAT allylation



Entry	x	y	Concentration (M)	T (°C)	Yield (5:5b:5b') %
1	2	4	0.75	70	0:35:52
2	2	2	0.75	70	0:37:44
3	1.5	2	0.75	70	10:59:26
4	1.1	2	0.75	70	25:57:15

Note: in this case, the double-derivatized products were separable and no α -oxygen derivatization was observed.

See the characterization part (p. S29) for details.

General procedures

General procedure A: Nucleophilic aromatic substitution

The amine (1 eq), the aromatic electrophile (1 or 2 eq), and potassium carbonate (5 eq) were weighted in an over-dried vial. The vial was sealed with a microwave septum and purged with nitrogen. Acetonitrile (0.2 M) was added, and the mixture was stirred at 85 °C for 16 h. Afterwards, the mixture was cooled down, and filtered, rinsing with ethyl acetate. The volatiles were removed *via* rotary evaporation, and the crude was purified with silica gel column chromatography to afford the desired product.

General procedure B: HAT cyanation

Adapted from a reported procedure.¹ The substrate (0.20 mmol, 1 eq), HAT reagent **1** (170 mg, 0.40 mmol, 2 eq), and tosyl cyanide (140 mg, 0.80 mmol, 4 eq) were weighted in an over-dried vial. The vial was sealed with a microwave septum and purged with nitrogen. Distilled trifluorotoluene (270 μ L, 0.75 M) was added and the mixture was stirred at 70 °C for 16 h. Afterwards, the mixture was cooled down and volatiles were removed *via* rotary evaporation. The crude was purified with silica gel column chromatography followed by reverse-phase column chromatography to afford the desired product.

General procedure C: HAT allylation

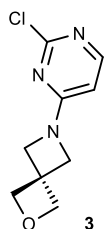
The substrate (0.20 mmol, 1 eq), HAT reagent **1** (0.30 mmol, 1.5 eq), and allylic sulfone **3** (0.40 mmol, 2 eq) were weighted in an over-dried vial. The vial was sealed with a microwave septum and purged with nitrogen. Distilled trifluorotoluene (270 μ L, 0.75 M) was added and the mixture was stirred at 70 °C for 16 h. Afterwards, the mixture was cooled down and volatiles were removed *via* rotary evaporation. The crude was purified with silica gel column chromatography followed by reverse-phase column chromatography to afford the desired product.

General procedure D: HAT vinylation

The substrate (0.20 mmol, 1 eq), HAT reagent **1** (0.40 mmol, 2 eq), and vinyl sulfone **21** (0.80 mmol, 4 eq) were weighted in an over-dried vial. The vial was sealed with a microwave septum and purged with nitrogen. Distilled trifluorotoluene (270 μ L, 0.75 M) was added and the mixture was stirred at 70 °C for 16 h. Afterwards, the mixture

was cooled down and volatiles were removed *via* rotary evaporation. The crude was purified with silica gel column chromatography followed by reverse-phase column chromatography to afford the desired product.

Substrates synthesis



Compound 3.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (300 mg, 1.04 mmol, 1 eq), 2,5-dichloropyrimidine (310 mg, 2.08 mmol, 2 eq), and potassium carbonate (720 mg, 5.21 mmol, 5 eq) in acetonitrile (5.2 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (290 mg, 1.37 mmol, 66% yield) as an amorphous white solid.

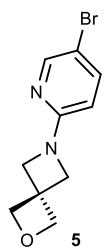
R_f 0.17 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 7.98 (d, *J* = 5.8 Hz, 1H), 6.05 (d, *J* = 5.9 Hz, 1H), 4.82 (s, 4H), 4.25 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 163.1, 161.0, 156.6, 100.7, 80.8, 59.5, 39.2.

IR (ATR, neat, cm⁻¹) 2939 (w), 2867 (w), 1580 (s), 1498 (s), 1352 (s), 1314 (m), 1144 (m), 968 (s), 812 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₉H₁₁ClN₃O [M+H]⁺ calc.: 212.0585; found: 212.0584.



Compound 5.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 5-bromo-2-fluoro-pyridine (305 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (441 mg, 1.73 mmol, 100% yield) as an amorphous white solid.

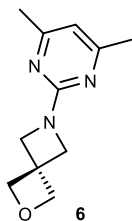
R_f 0.54 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.14 (dd, *J* = 2.5, 0.7 Hz, 1H), 7.49 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.17 (dd, *J* = 8.8, 0.7 Hz, 1H), 4.82 (s, 4H), 4.13 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 158.8, 148.9, 139.6, 108.1, 107.5, 81.2, 60.4, 39.0.

IR (ATR, neat, cm⁻¹) 2943 (m), 2872 (m), 2851 (m), 1578 (m), 1490 (m), 1400 (m), 1306 (m), 1089 (m), 966 (s), 813 (s).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₀H₁₂BrN₂O [M+H]⁺ calc.: 255.0128; found: 255.0127.



Compound 6.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 2-chloro-4,6-dimethyl-1,3-diazine (247 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product

(314 mg, 1.53 mmol, 88% yield) as an amorphous white solid.

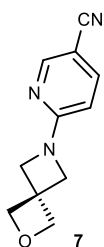
R_f 0.23 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 6.32 (s, 1H), 4.82 (s, 4H), 4.25 (s, 4H), 2.28 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 167.4, 163.1, 110.2, 81.4, 60.0, 38.7, 24.0.

IR (ATR, neat, cm⁻¹) 2863 (w), 1558 (s), 1497 (s), 1464 (s), 1381 (m), 1338 (m), 1210 (w), 972 (s), 789 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₁H₁₆N₃O [M+H]⁺ calc.: 206.1288; found: 206.1285.



Compound 7.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 6-chloronicotinonitrile (240 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (147 mg, 0.73 mmol, 42%

yield) as an amorphous white solid.

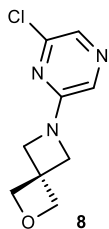
R_f 0.31 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.36 (dd, *J* = 2.2, 0.8 Hz, 1H), 7.57 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.22 (dd, *J* = 8.8, 0.8 Hz, 1H), 4.85 (s, 4H), 4.26 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 159.8, 153.2, 139.5, 118.6, 105.2, 97.1, 80.9, 59.9, 39.0.

IR (ATR, neat, cm⁻¹) 2209 (m), 1597 (s), 1543 (m), 1513 (m), 1438 (m), 1309 (m), 1109 (w), 967 (m), 827 (s).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₁H₁₂N₃O [M+H]⁺ calc.: 202.0975; found: 202.0974.



Compound 8.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 2,6-dichloro-pyrazine (258 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (282 mg, 1.33 mmol, 77% yield) as an amorphous white solid.

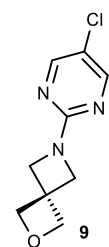
R_f 0.40 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 7.81 (s, 1H), 7.59 (s, 1H), 4.82 (s, 4H), 4.24 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 154.7, 147.3, 131.4, 127.4, 80.9, 60.3, 39.6.

IR (ATR, neat, cm⁻¹) 2945 (w), 2863 (w), 1567 (s), 1504 (s), 1465 (m), 1411 (m), 1315 (w), 1175 (s), 1106 (m), 989 (m), 973 (s), 836 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₉H₁₁ClN₃O [M+H]⁺ calc.: 212.0585; found: 212.0586.



Compound 9.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 2,5-dichloro-1,3-diazine (258 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (357 mg, 1.69 mmol, 97% yield) as an amorphous white solid.

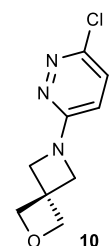
R_f 0.49 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.20 (s, 2H), 4.82 (s, 4H), 4.24 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 160.6, 156.2, 119.5, 81.1, 59.9, 38.6.

IR (ATR, neat, cm⁻¹) 2933 (m), 2864 (m), 1577 (s), 1508 (s), 1462 (s), 1385 (m), 1310 (w), 1214 (w), 1135 (m), 940 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₉H₁₁ClN₃O [M+H]⁺ calc.: 212.0585; found: 212.0584.



Compound 10.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 3,6-dichloro pyridazine (258 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate

mixture as eluent (0% to 100% ethyl acetate), affording the desired product (319 mg, 1.51 mmol, 87% yield) as an amorphous white solid.

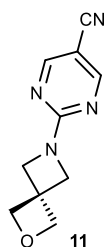
R_f 0.14 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 7.17 (d, *J* = 9.2 Hz, 1H), 6.52 (d, *J* = 9.3 Hz, 1H), 4.84 (s, 4H), 4.27 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 159.4, 147.3, 128.9, 114.3, 81.0, 60.5, 39.6.

IR (ATR, neat, cm⁻¹) 3040 (w), 2947 (m), 2872 (m), 2859 (w), 1588 (s), 1532 (m), 1525 (m), 1475 (s), 1320 (w), 1155 (m), 1085 (w), 967 (s), 848 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₉H₁₁ClN₃O [M+H]⁺ calc.: 212.0585; found: 212.0588.



Compound 11.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (100 mg, 0.35 mmol, 1 eq), 2-chloro-5-pyrimidinecarbonitrile (97 mg, 0.69 mmol, 2 eq), and potassium carbonate (240 mg, 1.73 mmol, 5 eq) in acetonitrile (1.7 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (76 mg, 0.38 mmol,

54% yield) as an amorphous white solid.

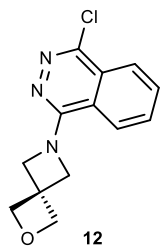
R_f 0.34 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.47 (s, 2H), 4.85 (s, 4H), 4.36 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 161.0, 160.5, 116.6, 96.7, 80.8, 59.6, 38.7.

IR (ATR, neat, cm⁻¹) 2949 (w), 2877 (w), 2216 (m), 1600 (s), 1558 (s), 1509 (m), 1400 (m), 1228 (m), 959 (w).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₀H₁₁N₄O [M+H]⁺ calc.: 203.0927; found: 203.0927.



Compound 12.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 1,4-dichlorophthalazine (345 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.34 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired

product (256 mg, 0.98 mmol, 56% yield) as an amorphous white solid.

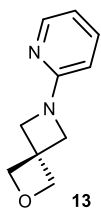
R_f 0.20 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.22 – 8.12 (m, 1H), 7.95 – 7.76 (m, 3H), 4.89 (s, 4H), 4.65 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 156.9, 147.5, 132.6, 131.9, 126.9, 125.9, 123.9, 121.0, 81.2, 63.4, 40.2.

IR (ATR, neat, cm⁻¹) 2936 (w), 2864 (m), 1570 (w), 1499 (s), 1443 (s), 1351 (s), 1317 (m), 1295 (w), 974 (m), 766 (m).

HRMS (ESI-TOF, m/z) calcd. for C₁₃H₁₃ClN₃O [M+H]⁺ calc.: 262.0742; found: 262.0736.



Compound 13.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 2-fluoropyridine (168 mg, 149 μL, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (123 mg, 0.70 mmol, 40% yield) as a colorless oil.

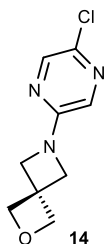
R_f 0.18 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.13 (ddd, *J* = 5.1, 1.9, 0.9 Hz, 1H), 7.44 (ddd, *J* = 8.3, 7.2, 1.9 Hz, 1H), 6.61 (ddd, *J* = 7.2, 5.1, 1.0 Hz, 1H), 6.28 (dt, *J* = 8.4, 1.0 Hz, 1H), 4.83 (s, 4H), 4.15 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 160.4, 148.3, 137.3, 113.4, 106.2, 81.4, 60.3, 39.1.

IR (ATR, neat, cm⁻¹) 2931 (w), 2862 (m), 1591 (s), 1558 (w), 1489 (m), 1469 (m), 1438 (s), 1345 (m), 1149 (w), 974 (m), 774 (m).

HRMS (ESI-TOF, m/z) calcd. for C₁₀H₁₃N₂O [M+H]⁺ calc.: 177.1022; found: 177.1026.



Compound 14.

Prepared following general procedure A, using 2-oxa-6-azaspiro[3.3]heptane hemioxalate (250 mg, 0.87 mmol, 1 eq), 3,6-dichloropyrazine (258 mg, 1.73 mmol, 2 eq), and potassium carbonate (600 mg, 4.34 mmol, 5 eq) in acetonitrile (4.3 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (304 mg, 1.44 mmol, 83% yield) as an amorphous white solid.

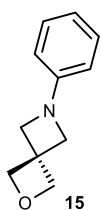
R_f 0.57 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 7.99 (d, *J* = 1.4 Hz, 1H), 7.48 (d, *J* = 1.4 Hz, 1H), 4.82 (s, 4H), 4.20 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 154.3, 141.5, 137.0, 128.6, 81.0, 60.4, 39.6.

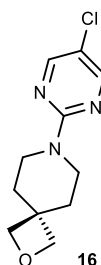
IR (ATR, neat, cm⁻¹) 2941 (m), 2920 (m), 2864 (s), 1569 (s), 1510 (s), 1490 (s), 1474 (s), 1354 (m), 1312 (m), 1198 (m), 1154 (s), 1000 (m), 965 (s), 774 (m).

HRMS (ESI-TOF, m/z) calcd. for C₉H₁₁ClN₃O [M+H]⁺ calc.: 212.0585; found: 212.0583.



Compound 15.

Bromobenzene (130 mg, 87 μ L, 0.83 mmol, 1 eq), 2-oxa-6-azaspiro[3.3]heptane hemioxalate (263 mg, 0.91 mmol, 1.1 eq), Pd₂(dba)₃ (38 mg, 0.04 mmol, 5 mol %), Xphos (40 mg, 0.08 mmol, 10 mol %), and cesium carbonate (1.35 g, 4.14 mmol, 5 eq) were added in a vial. The vial was sealed with a microwave cap and purged with nitrogen. Anhydrous toluene (8.3 mL, 0.1 M) was added, and the mixture was stirred at 100 °C for 16 h. Afterwards, the vial was cooled down to room temperature and the mixture was filtered through a pad of celite, rinsing with ethyl acetate. The solvents were removed *via* rotary evaporation, and the crude was purified with silica gel flash column chromatography using a cyclohexane/ethyl acetate mixture as eluent (0% to 50% ethyl acetate), affording the desired product (136 mg, 0.78 mmol, 94% yield) as an amorphous white solid. The analytical data is consistent with reported literature.⁸



Compound 16.

Prepared following general procedure A, using 2-oxa-7-azaspiro[3.5]nonane hemioxalate (210 mg, 0.61 mmol, 1 eq), 2,5-dichloro-1,3-diazine (182 mg, 1.22 mmol, 2 eq), and potassium carbonate (421 mg, 3.05 mmol, 5 eq) in acetonitrile (3.05 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 50% ethyl acetate), affording the desired product (282 mg, 1.18 mmol, 97% yield) as an amorphous white solid.

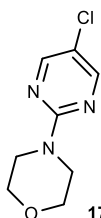
R_f 0.33 (*c*-hexane:EtOAc = 3:1, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.20 (s, 1H), 4.48 (s, 2H), 3.75 – 3.67 (m, 2H), 1.92 – 1.85 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 159.9, 156.0, 118.1, 81.7, 41.4, 39.2, 34.6.

IR (ATR, neat, cm⁻¹) 2862 (m), 1581 (s), 1525 (m), 1501 (s), 1459 (m), 1398 (w), 1356 (s), 1301 (m), 1251 (s), 1170 (w), 1137 (w), 969 (m), 940 (m), 885 (m).

HRMS (ESI-TOF, m/z) calcd. for C₁₁H₁₅ClN₃O [M+H]⁺ calc.: 240.0898; found: 240.0895.



Compound 17.

Prepared following general procedure A, using morpholine (100 mg, 99 μ L, 1.15 mmol, 1 eq), 2,5-dichloro-1,3-diazine (171 mg, 1.15 mmol, 1 eq), and potassium carbonate (397 mg, 2.87 mmol, 2.5 eq) in acetonitrile (5.7 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as

eluent (0% to 50% ethyl acetate), affording the desired product (228 mg, 1.14 mmol, >99% yield) as an amorphous white solid.

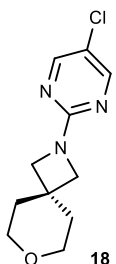
R_f 0.56 (*c*-hexane:EtOAc = 3:1, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 2H), 3.74 – 3.64 (m, 8H).

¹³C NMR (101 MHz, CDCl₃) δ 160.0, 156.0, 118.8, 66.8, 44.6.

IR (ATR, neat, cm⁻¹) 2963 (w), 2854 (w), 1581 (s), 1528 (m), 1488 (s), 1445 (s), 1391 (w), 1356 (s), 1299 (w), 1259 (s), 1168 (w), 1140 (w), 1117 (m), 957 (m), 787 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₈H₁₁ClN₃O [M+H]⁺ calc.: 200.0585; found: 200.0585.



Compound 18.

Prepared following general procedure A, using 7-oxa-2-azaspiro[3.5]nonane hemioxalate (200 mg, 0.58 mmol, 1 eq), 2,5-dichloro-1,3-diazine (173 mg, 1.16 mmol, 2 eq), and potassium carbonate (401 mg, 2.90 mmol, 5 eq) in acetonitrile (2.9 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (176 mg, 0.73 mmol,

63% yield) as an amorphous white solid.

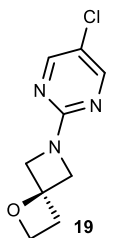
R_f 0.58 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 2H), 3.86 (s, 4H), 3.68 – 3.61 (m, 4H), 1.86 – 1.79 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 160.8, 156.2, 118.9, 65.0, 60.4, 36.4, 33.6.

IR (ATR, neat, cm⁻¹) 2968 (w), 2931 (w), 2863 (w), 1572 (s), 1523 (s), 1511 (s), 1476 (m), 1389 (w), 1257 (w), 878 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₁H₁₅ClN₃O [M+H]⁺ calc.: 240.0898; found: 240.0895.



Compound 19.

Prepared following general procedure A, using 1-oxa-6-azaspiro[3.3]heptane hemioxalate (200 mg, 0.69 mmol, 1 eq), 2,5-dichloro-1,3-diazine (207 mg, 1.39 mmol, 2 eq), and potassium carbonate (4.79 mg, 3.47 mmol, 5 eq) in acetonitrile (3.5 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate), affording the desired product (156 mg, 0.74 mmol, 53% yield) as an amorphous white solid.

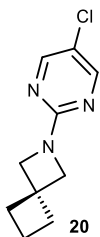
R_f 0.58 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 2H), 4.57 (t, *J* = 7.5 Hz, 2H), 4.36 – 4.24 (m, 4H), 2.91 (t, *J* = 7.5 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 160.7, 156.3, 119.4, 83.3, 66.6, 65.0, 32.1.

IR (ATR, neat, cm⁻¹) 2922 (w), 2896 (w), 1575 (s), 1522 (s), 1496 (s), 1452 (s), 1378 (m), 1286 (w), 1246 (m), 1131 (m), 1118 (m), 973 (w), 951 (m), 785 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₉H₁₁ClN₃O [M+H]⁺ calc.: 212.0585; found: 212.0582.



Compound 20.

Prepared following general procedure A, using 2-azaspiro[3.3]heptane hemioxalate (200 mg, 0.70 mmol, 1 eq), 2,5-dichloro-1,3-diazine (210 mg, 1.41 mmol, 2 eq), and potassium carbonate (486 mg, 3.52 mmol, 5 eq) in acetonitrile (3.5 mL, 0.2 M). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 30% ethyl acetate), affording the desired product (251 mg, 1.20 mmol, 85% yield) as an amorphous white solid.

R_f 0.63 (*c*-hexane:EtOAc = 3:1, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 2H), 4.08 (s, 4H), 2.23 (t, *J* = 7.6 Hz, 4H), 1.95 – 1.83 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 160.6, 156.2, 118.6, 62.9, 38.6, 33.3, 16.3.

IR (ATR, neat, cm⁻¹) 2975 (m), 2953 (m), 2936 (m), 2866 (m), 1574 (s), 1529 (s), 1472 (m), 1381 (m), 1313 (m), 1130 (m), 936 (w), 787 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₀H₁₃ClN₃ [M+H]⁺ calc.: 210.0793; found: 210.0790.

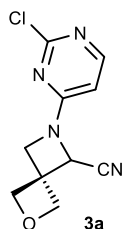
pKa, logP and solubility measurements table

Structure	Theoretical pKa*	Measured pKa (in Water)	Theoretical Log P*	Measured Log P	Theoretical Solubility*	Measured Solubility
5	5.89	4.18	1.17	1.86	68 mM	35 mM
6	6.28	4.50	1.51	0.90	3 mM	32 μ M
7	4.81	2.69	0.36	0.42	79 mM	50 mM
9	3.34	2.82	1.42	1.31	2.35 mM	2.2 mM
11	2.06	2.32	0.63	0.85	98 μ M	88 μ M
12	5.66	4.62	1.26	1.54	8 mM	10 mM
13	5.96	6.12	1.13	1.02	66 mM	103.6 mM
14	2.26	2.01	0.77	0.80	276 mM	100 mM
15	2.65	2.95	1.06	1.60	74 mM	49 mM
16	3.52	2.50	2.03	2.54	805 μ M	802 μ M
17	3.23	3.15	1.35	1.08	5.4 mM	2 mM
18	3.5	2.5	2.03	2.39	805 μ M	315 μ M
19	3.23	3.30	1.51	1.45	2 mM	504 μ M
20	3.64	3.30	-	-	527 μ M	505 μ M

*Theoretical values calculated using ACD Prediction

(<https://www.acdlabs.com/products/percepta-platform/physchem-suite/>)

HAT cyanation products



Compound 3a.

Prepared following general procedure B, using compound **3** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (30 mg, 0.13 mmol, 63% yield) was isolated as an amorphous white solid, alongside the double derivatized products (19 mg, 0.07 mmol, 36% yield).

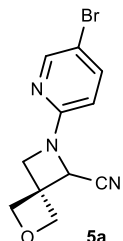
R_f 0.19 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, *J* = 5.7 Hz, 1H), 6.28 (d, *J* = 5.7 Hz, 1H), 5.13 (d, *J* = 8.0 Hz, 1H), 5.07 (s, 1H), 4.89 (d, *J* = 8.0 Hz, 1H), 4.86 (s, 2H), 4.38 (d, *J* = 9.1 Hz, 1H), 4.25 (d, *J* = 9.1 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 162.6, 161.1, 158.1, 114.3, 101.5, 78.8, 77.6, 58.7, 57.2, 42.3.

IR (ATR, neat, cm⁻¹) 1574 (s), 1537 (m), 1487 (m), 1459 (m), 1350 (s), 1305 (w), 1153 (w), 971 (s), 868 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₀H₁₀ClN₄O [M+H]⁺ calc.: 237.0538; found: 237.0531.



Compound 5a.

Prepared following general procedure B, using compound **5** (51 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 80% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (41 mg, 0.15 mmol, 73% yield) was isolated as an amorphous white solid.

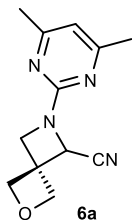
R_f 0.61 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.26 (dd, *J* = 2.4, 0.8 Hz, 1H), 7.63 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.35 (dd, *J* = 8.7, 0.8 Hz, 1H), 5.18 (d, *J* = 7.8 Hz, 1H), 4.91 (m, 3H), 4.81 (s, 3H), 4.26 (d, *J* = 8.3, Hz, 1H), 4.07 (d, *J* = 8.2 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 156.6, 149.3, 140.3, 115.7, 111.1, 108.2, 78.9, 78.2, 59.3, 57.7, 42.0.

IR (ATR, neat, cm⁻¹) 2948 (w), 2872 (w), 1579 (s), 1552 (w), 1462 (s), 1385 (s), 1339 (m), 1304 (w), 1294 (w), 1091 (m), 976 (m), 736 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₁H₁₁BrN₃O [M+H]⁺ calc.: 280.0080; found: 280.0084.



Compound 6a.

Prepared following general procedure B, using compound **6** (41 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (29 mg, 0.13 mmol, 63% yield) was isolated as an amorphous white solid.

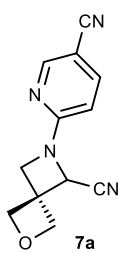
R_f 0.42 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 6.50 (s, 1H), 5.17 (d, *J* = 7.6 Hz, 1H), 4.99 (s, 1H), 4.89 (d, *J* = 7.7 Hz, 1H), 4.81 (s, 2H), 4.35 (dd, *J* = 9.0, 0.9 Hz, 1H), 4.23 (d, *J* = 9.0 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 168.0, 161.5, 116.1, 112.4, 79.3, 78.2, 58.8, 57.6, 41.6, 24.0.

IR (ATR, neat, cm⁻¹) 2951 (w), 2974 (w), 1582 (s), 1558 (s), 1444 (s), 1382 (m), 1328 (m), 1297 (w), 978 (s).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₂H₁₅N₄O [M+H]⁺ calc.: 231.1240; found: 231.1236.



Compound 7a.

Prepared following general procedure B, using compound **7** (40 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (41 mg, 0.18 mmol, 91% yield) was isolated as an amorphous white solid.

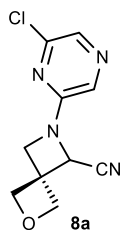
R_f 0.41 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.48 (dd, *J* = 2.2, 0.8 Hz, 1H), 7.73 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.44 (dd, *J* = 8.6, 0.8 Hz, 1H), 5.18 (d, *J* = 7.9 Hz, 1H), 5.05 (s, 1H), 4.92 (d, *J* = 7.9 Hz, 1H), 4.85 (s, 2H), 4.38 (dd, *J* = 8.6, 1.0 Hz, 1H), 4.22 (d, *J* = 8.7 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 158.5, 153.0, 140.5, 117.7, 115.0, 106.0, 100.4, 78.9, 77.9, 59.0, 57.5, 42.03.

IR (ATR, neat, cm⁻¹) 2949 (w), 2875 (w), 2220 (m), 1594 (s), 1496 (s), 1409 (m), 1308 (m), 1212 (w), 1158 (w), 977 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₂H₁₁N₄O [M+H]⁺ calc.: 227.0927; found: 227.0926.



Compound 8a.

Prepared following general procedure B, using compound **8** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (42 mg, 0.18 mmol, 89% yield) was isolated as a colorless oil.

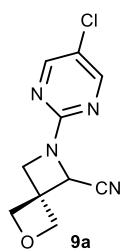
R_f 0.46 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1H), 7.81 (s, 1H), 5.18 (d, *J* = 7.9 Hz, 1H), 5.03 (s, 1H), 4.92 (d, *J* = 7.9 Hz, 1H), 4.84 (s, 2H), 4.41 (dd, *J* = 8.6, 1.0 Hz, 1H), 4.23 (d, *J* = 8.6 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 153.0, 147.5, 134.8, 127.7, 114.8, 78.8, 77.9, 59.5, 57.8, 42.6.

IR (ATR, neat, cm⁻¹) 2949 (w), 2875 (w), 1564 (s), 1511 (s), 1455 (s), 1410 (s), 1344 (w), 1175 (m), 1111 (m), 977 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₀H₁₀ClN₄O [M+H]⁺ calc.: 237.0538; found: 237.0533.



Compound 9a.

Prepared following general procedure B, using compound **9** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 80% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (46 mg, 0.19 mmol, 97% yield) was isolated as an amorphous white solid.

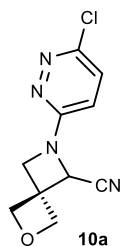
R_f 0.59 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.34 (s, 2H), 5.15 (d, *J* = 7.8 Hz, 1H), 5.00 (s, 1H), 4.90 (d, *J* = 7.8 Hz, 1H), 4.83 (s, 2H), 4.35 (dd, *J* = 9.3, 1.0 Hz, 1H), 4.25 (d, *J* = 9.2 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 159.5, 156.6, 122.4, 115.4, 79.1, 78.0, 58.9, 57.7, 41.7.

IR (ATR, neat, cm⁻¹) 1576 (s), 1521 (m), 1500 (s), 1384 (m), 1282 (w), 1132 (w), 973 (m), 943 (s).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₀H₁₀ClN₄O [M+H]⁺ calc.: 237.0538; found: 237.0539.



Compound 10a.

Prepared following general procedure B, using compound **10** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired

product (36 mg, 0.15 mmol, 76% yield) was isolated as an amorphous white solid, alongside the double derivatized products (12 mg, 0.05 mmol, 23% yield).

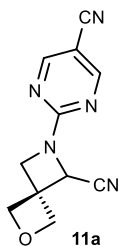
R_f 0.27 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, Acetone-d₆) δ 7.55 (d, *J* = 9.3 Hz, 1H), 7.08 (d, *J* = 9.2 Hz, 1H), 5.44 (s, 1H), 5.06 (d, *J* = 7.5 Hz, 1H), 4.97 (d, *J* = 7.5 Hz, 1H), 4.88 (d, *J* = 7.5 Hz, 1H), 4.80 (d, *J* = 7.5 Hz, 1H), 4.47 (d, *J* = 8.4 Hz, 1H), 4.38 (d, *J* = 8.3 Hz, 1H).

¹³C NMR (75 MHz, Acetone-d₆) δ 160.2, 149.7, 130.1, 116.9, 116.7, 79.0, 78.4, 60.3, 58.6, 43.4.

IR (ATR, neat, cm⁻¹) 2876 (w), 1580 (m), 1534 (w), 1433 (s), 1348 (w), 1112 (m), 977 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₀H₁₀CIN₄O [M+H]⁺ calc.: 237.0538; found: 237.0534.



Compound 11a.

Prepared following general procedure B, using compound **11** (40 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (25 mg, 0.11 mmol, 55% yield) was isolated as an amorphous white solid, alongside the double

derivatized products (18 mg, 0.07 mmol, 36%).

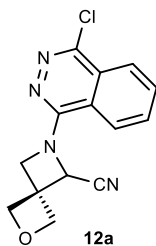
R_f 0.43 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.62 (s, 2H), 5.21 – 5.09 (m, 2H), 4.96 – 4.81 (m, 3H), 4.52 – 4.34 (m, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 161.3, 160.2, 115.6, 114.5, 99.9, 79.0, 77.4, 58.7, 57.5, 41.9.

IR (ATR, neat, cm⁻¹) 2925 (w), 2874 (w), 2221 (m), 1738 (w), 1595 (s), 1519 (s), 1454 (m), 1226 (m), 958 (w).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₁H₁₀N₅O [M+H]⁺ calc.: 228.0880; found: 228.0878.



Compound 12a.

Prepared following general procedure B, using compound **12** (52 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile).

The desired product (40 mg, 0.14 mmol, 70% yield) was isolated as a white foam, alongside the double derivatized products (18 mg, 0.06 mmol, 29% yield).

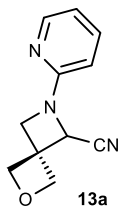
R_f 0.32 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.30 – 8.18 (m, 1H), 8.03 – 7.80 (m, 3H), 5.63 (s, 1H), 5.32 (d, *J* = 7.7 Hz, 1H), 5.02 (d, *J* = 7.7 Hz, 1H), 4.91 – 4.83 (m, 2H), 4.79 (d, *J* = 7.6 Hz, 1H), 4.45 (d, *J* = 8.2 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 155.5, 150.4, 133.5, 132.9, 127.1, 126.3, 123.4, 120.9, 115.6, 78.6, 63.9, 57.7, 42.6. (Note: The peak at 78.6 ppm is two different carbons, as it can be seen by HSQC).

IR (ATR, neat, cm⁻¹) 2874 (w), 1571 (w), 1494 (s), 1417 (s), 1374 (m), 1295 (m), 1097 (w), 978 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₄H₁₂ClN₄O [M+H]⁺ calc.: 287.0694; found: 287.0695.



Compound 13a.

Prepared following general procedure B, using compound **13** (35 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired

product (12 mg, 0.06 mmol, 30% yield) was isolated as a colorless oil, alongside the double derivatized products (11 mg, 0.05 mmol, 24% yield).

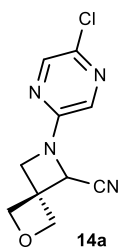
R_f 0.30 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.23 (ddd, *J* = 5.1, 1.8, 0.9 Hz, 1H), 7.57 (ddd, *J* = 8.3, 7.3, 1.8 Hz, 1H), 6.81 (ddd, *J* = 7.3, 5.1, 0.9 Hz, 1H), 6.46 (dt, *J* = 8.3, 0.9 Hz, 1H), 5.20 (d, *J* = 7.7 Hz, 1H), 4.98 – 4.87 (m, 2H), 4.81 (s, 2H), 4.30 (dd, *J* = 8.3, 0.9 Hz, 1H), 4.11 (d, *J* = 8.3 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 158.0, 148.3, 138.0, 116.0, 115.9, 107.0, 79.0, 78.4, 59.3, 57.7, 42.0.

IR (ATR, neat, cm⁻¹) 2948 (w), 2873 (w), 1594 (s), 1563 (m), 1478 (s), 1436 (s), 1341 (m), 1304 (w), 1140 (w), 977 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₁H₁₂N₃O [M+H]⁺ calc.: 202.0975; found: 202.0975.



Compound 14a.

Prepared following general procedure B, using compound **14** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 80% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (38 mg, 0.16 mmol, 80% yield) was isolated as an amorphous white solid, alongside the double derivatized products (10 mg, 0.04 mol, 19% yield).

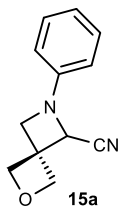
R_f 0.54 (*c*-hexane:EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.16 (d, *J* = 1.5 Hz, 1H), 7.69 (d, *J* = 1.5 Hz, 1H), 5.18 (d, *J* = 7.8 Hz, 1H), 5.01 – 4.88 (m, 2H), 4.83 (s, 2H), 4.37 (dd, *J* = 8.4, 1.0 Hz, 1H), 4.18 (d, *J* = 8.3 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 152.5, 141.9, 140.1, 129., 115.1, 78.7, 78.0, 59.5, 57.9, 42.6.

IR (ATR, neat, cm⁻¹) 2950 (w), 2875 (w), 1567 (s), 1519 (m), 1471 (s), 1386 (m), 1350 (m), 1319 (w), 1168 (w), 1136 (w), 1110 (m), 982 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₀H₁₀ClN₄O [M+H]⁺ calc.: 237.0538; found: 237.0536.



Compound 15a.

Prepared following general procedure B, using compound **15** (35 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 50% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (31 mg, 0.15 mmol, 77% yield) was isolated as an amorphous white solid.

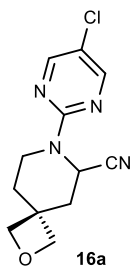
R_f 0.26 (*c*-hexane:EtOAc = 3:1, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 7.38 – 7.22 (m, 2H), 6.98 – 6.86 (m, 1H), 6.65 – 6.54 (m, 2H), 5.20 (d, *J* = 7.6 Hz, 1H), 4.97 – 4.86 (m, 1H), 4.79 (s, 2H), 4.67 (d, *J* = 0.8 Hz, 1H), 4.20 (dd, *J* = 7.7, 0.9 Hz, 1H), 3.94 (d, *J* = 7.7 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 148.1, 129.5, 120.6, 116.0, 112.5, 78.7, 78.6, 60.2, 59.2, 42.1.

IR (ATR, neat, cm⁻¹) 2948 (w), 2872 (w), 1736 (w), 1599 (s), 1500 (s), 1364 (w), 1330 (m), 1180 (w), 978 (m), 754 (s).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₂H₁₃N₂O [M+H]⁺ calc.: 201.1022; found: 201.1022.



Compound 16a.

Prepared following general procedure B, using compound **16** (48 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 50% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (19 mg, 0.07 mmol, 36% yield) was isolated as an amorphous white solid, alongside recovered starting material (9 mg, 0.04 mol, 20% yield).

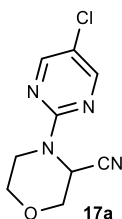
R_f 0.22 (*c*-hexane:EtOAc = 3:1, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 2H), 5.83 (dt, *J* = 5.8, 1.7 Hz, 1H), 5.02 (dd, *J* = 6.6, 1.5 Hz, 1H), 4.74 (ddt, *J* = 14.2, 4.2, 1.7 Hz, 1H), 4.63 (d, *J* = 6.5 Hz, 1H), 4.51 (d, *J* = 6.0 Hz, 1H), 4.37 (d, *J* = 6.0 Hz, 1H), 3.08 (td, *J* = 13.6, 2.7 Hz, 1H), 2.56 (dt, *J* = 13.9, 2.2 Hz, 1H), 2.43 (dq, *J* = 13.5, 2.6 Hz, 1H), 1.87 (dd, *J* = 13.9, 5.8 Hz, 1H), 1.72 (tdd, *J* = 13.3, 4.7, 1.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 159.1, 156.3, 121.4, 117.9, 81.8, 80.6, 42.2, 38.5, 37.9, 35.7, 34.0.

IR (ATR, neat, cm⁻¹) 2931 (w), 2866 (w), 1579 (s), 1536 (m), 1475 (m), 1440 (s), 1361 (m), 1209 (m), 1175 (m), 981 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₂H₁₄ClN₄O [M+H]⁺ calc.: 265.0851; found: 265.0847.



Compound 17a.

Prepared following general procedure B, using compound **17** (40 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 50% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (39 mg, 0.17 mmol, 87% yield) was isolated as an amorphous white solid.

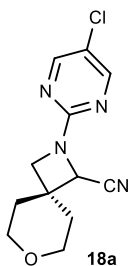
R_f 0.44 (*c*-hexane:EtOAc = 3:1, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.37 (s, 2H), 5.45 (d, *J* = 2.8 Hz, 1H), 4.40 (ddt, *J* = 13.6, 2.7, 1.2 Hz, 1H), 4.24 – 4.16 (m, 1H), 4.10 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.75 (dd, *J* = 11.9, 3.1 Hz, 1H), 3.62 (td, *J* = 11.9, 2.9 Hz, 1H), 3.31 (ddd, *J* = 13.7, 12.1, 3.6 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 159.1, 156.4, 122.0, 116.9, 67.7, 66.8, 44.8, 41.7.

IR (ATR, neat, cm⁻¹) 1577 (m), 1536 (m), 1435 (s), 1387 (w), 1297 (w), 1263 (w), 1171 (m), 1121 (m), 1075 (m), 950 (s).

HRMS (ESI-TOF, *m/z*) calcd. for C₉H₁₀ClN₄O [M+H]⁺ calc.: 225.0538; found: 225.0537.



Compound 18a.

Prepared following general procedure B, using compound **18** (48 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 80% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (53 mg, 0.20 mmol, >99% yield) was isolated as an amorphous white solid.

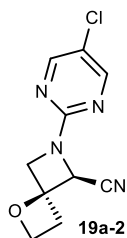
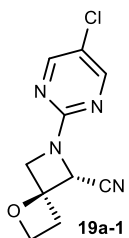
R_f 0.14 (*c*-hexane:EtOAc = 3:1, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 2H), 4.60 (s, 1H), 4.02 – 3.83 (m, 3H), 3.76 (ddd, *J* = 12.0, 5.7, 3.9 Hz, 1H), 3.62 (dddd, *J* = 17.0, 11.8, 8.3, 3.3 Hz, 2H), 2.15 (ddd, *J* = 12.6, 8.3, 3.9 Hz, 1H), 2.02 (dddd, *J* = 13.6, 5.8, 3.2, 1.4 Hz, 1H), 1.97 – 1.81 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 159.7, 156.6, 121.8, 115.9, 64.5, 64.4, 59.6, 58.2, 37.6, 36.3, 33.8.

IR (ATR, neat, cm⁻¹) 1574 (s), 1536 (m), 1488 (s), 1464 (s), 1386 (w), 1229 (m), 1128 (w), 1104 (m), 788 (w), 678 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₂H₁₄ClN₄O [M+H]⁺ calc.: 265.0851; found: 265.0845.



Compounds 19a-1 and 19a-2.

Prepared following general procedure B, using compound **19** (42 mg, 0.20 mmol, 1 eq).

The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 60% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). Compound **19a-1** (19 mg, 0.08 mmol, 40% yield) and compound **19a-2** (17 mg, 0.07 mol, 36% yield) were isolated independently as amorphous white solids.

19a-1:

R_f 0.24 (*c*-hexane:EtOAc = 3:1, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 2H), 4.95 (s, 1H), 4.66 (ddt, *J* = 22.9, 8.5, 6.0 Hz, 2H), 4.39 – 4.23 (m, 2H), 3.35 (ddd, *J* = 12.5, 8.4, 6.0 Hz, 1H), 3.03 (ddd, *J* = 12.5, 8.6, 6.8 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 160.3, 156.6, 122.4, 115.8, 84.4, 67.5, 64.3, 62.5, 29.7.

IR (ATR, neat, cm⁻¹) 2901 (w), 1575 (s), 1536 (m), 1487 (s), 1473 (s), 1453 (s), 1381 (w), 1329 (w), 1249 (w), 1099 (m), 972 (m), 945 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₀H₁₀ClN₄O [M+H]⁺ calc.: 237.0538; found: 237.0539.

19a-2:

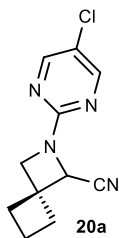
R_f 0.10 (*c*-hexane:EtOAc = 3:1, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 2H), 5.05 (s, 1H), 4.76 (ddd, *J* = 8.2, 7.0, 5.9 Hz, 1H), 4.65 (dt, *J* = 8.6, 5.9 Hz, 1H), 4.42 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.29 (d, *J* = 10.2 Hz, 1H), 3.05 (ddd, *J* = 12.3, 8.6, 7.0 Hz, 1H), 2.92 (ddd, *J* = 12.3, 8.2, 5.8 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 159.2, 156.6, 122.0, 114.3, 83.1, 67.5, 64.1, 62.7, 31.6.

IR (ATR, neat, cm⁻¹) 1573 (m), 1540 (m), 1463 (s), 1444 (s), 1380 (m), 1249 (w), 1138 (m), 933 (s), 858 (s), 793 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₀H₁₀ClN₄O [M+H]⁺ calc.: 237.0538; found: 237.0535.

**Compound 20a.**

Prepared following general procedure B, using compound **20** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 35% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). A white solid was isolated (48 mg), containing an inseparable mixture of the desired product (0.16 mmol, 81% yield) and the double derivatized product (0.04 mmol, 19% yield).

R_f 0.48 (*c*-hexane:EtOAc = 3:1, UV, KMnO₄).

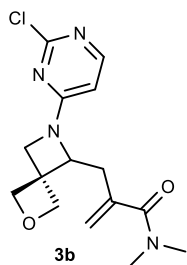
¹H NMR (400 MHz, CDCl₃) **20a**: δ 8.26 (s, 2H), 4.71 (s, 1H), 4.09 (d, *J* = 8.5 Hz, 1H), 3.99 (d, *J* = 8.5 Hz, 1H), 2.58 (dd, *J* = 12.4, 7.9 Hz, 1H), 2.28 – 2.18 (m, 3H), 1.91 (p, *J* = 7.7 Hz, 2H); **20a-double**: δ 8.37 (s, 2H), 4.81 (s, 2H), 2.72 – 2.58 (m, 2H), 2.39 – 2.24 (m, 2H), 2.01 (p, *J* = 7.8 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) **20a**: δ 159.8, 156.5, 121.6, 116.4, 61.8, 59.4, 41.8, 32.7, 30.7, 16.0; **20a-double**: δ 157.5, 156.8, 124.0, 115.0, 58.4, 44.8, 30.1, 15.8.

IR (ATR, neat, cm⁻¹) 2941 (w), 1574 (s), 1535 (m), 1457 (s), 1379 (w), 1325 (w), 1132 (w), 935 (w), 790 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₁H₁₂ClN₄ [M+H]⁺ calc.: 235.0745; found: 235.0740.

HAT allylation products



Compound 3b.

Prepared following general procedure C, using compound **3** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (**3b**, 30 mg, 0.09 mmol, 46% yield) was isolated as a colorless oil, alongside recovered starting material (9 mg, 0.04 mmol, 20% yield), and double derivatized products (9 mg, 0.02 mmol, 10% yield).

R_f 0.39 (EtOAc:MeOH = 10:1, UV, KMnO₄).

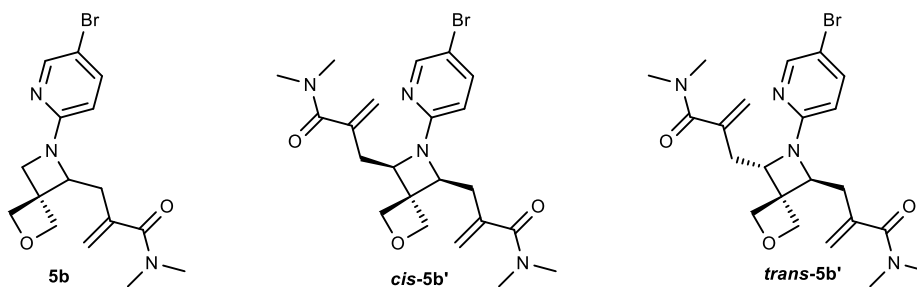
¹H NMR (300 MHz, CDCl₃) δ 8.00 (d, *J* = 5.9 Hz, 1H), 6.32 (s, 1H), 5.42 (s, 1H), 5.29 (d, 1H), 5.07 (d, *J* = 7.4 Hz, 1H), 4.76 (q, *J* = 6.9 Hz, 2H), 4.67 (d, *J* = 7.4 Hz, 1H), 4.59 (dd, *J* = 8.0, 4.5 Hz, 1H), 4.32 (d, *J* = 9.7 Hz, 1H), 4.13 (d, *J* = 9.7 Hz, 1H), 3.16 – 2.83 (m, 8H).

¹³C NMR (75 MHz, CDCl₃) δ 170.9, 163.9, 160.7, 156.8, 140.4, 119.1, 101.9, 81.2, 76.6, 67.7, 59.0, 43.3, 38.9, 35.7, 34.9.

IR (ATR, neat, cm⁻¹) 2970 (w), 2939 (w), 2870 (w), 1738 (m), 1615 (m), 1583 (s), 1494 (m), 1393 (w), 1352 (s), 1217 (m), 1116 (w), 970 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₅H₂₀ClN₄O₂ [M+H]⁺ calc.: 323.1269; found: 323.1264.

Compounds 5b, *cis*-5b', and *trans*-5b'.



Prepared following general procedure C, using compound **5** (51 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product **5b** (43 mg, 0.12 mmol, 59% yield) was isolated as an amorphous white solid,

alongside recovered starting material (5 mg, 0.02 mmol, 10% yield), and double derivatized products *cis-5b'* (12 mg, 0.03 mmol, 13% yield) and *trans-5b'* (13 mg, 0.03 mmol, 14% yield).

5b:

R_f 0.65 (EtOAc:MeOH = 10:1, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.13 – 8.06 (m, 1H), 7.47 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.39 – 6.28 (m, 1H), 5.45 (s, 1H), 5.26 (s, 1H), 5.10 (d, *J* = 7.2 Hz, 1H), 4.74 – 4.62 (m, 3H), 4.34 (dd, *J* = 9.0, 3.8 Hz, 1H), 4.18 (d, *J* = 9.0 Hz, 1H), 3.93 (d, *J* = 8.8 Hz, 1H), 3.18 – 2.88 (m, 7H), 2.77 (dd, *J* = 15.4, 9.0 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 171.1, 159.1, 148.7, 140.7, 139.5, 118.3, 108.5, 108.4, 82.0, 77.2, 67.3, 59.7, 43.0, 39.0, 36.5, 34.9.

IR (ATR, neat, cm⁻¹) 2359 (s), 2342 (s), 1639 (m), 1614 (s), 1580 (s), 1476 (s), 1460 (s), 1390 (s), 1342 (w), 1297 (w), 1090 (m), 974 (m), 813 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₆H₂₁BrN₃O₂ [M+H]⁺ calc.: 366.0812; found: 366.0809.

***Cis-5b'*:**

R_f 0.48 (EtOAc:MeOH = 10:1, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J* = 2.4 Hz, 1H), 7.50 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.64 (d, *J* = 8.9 Hz, 1H), 5.50 (s, 2H), 5.29 (s, 2H), 4.92 (s, 2H), 4.68 (s, 2H), 4.24 (dd, *J* = 9.5, 4.1 Hz, 2H), 3.21 – 2.93 (m, 16H), 2.72 (dd, *J* = 15.6, 9.4 Hz, 2H).

¹³C NMR ¹³C NMR (101 MHz, CDCl₃) δ 171.4, 148.6, 140.8, 139.8, 118.2, 109.3, 109.1, 81.5, 72.4, 66.8, 47.1, 39.2, 37.8, 35.1.

HRMS (ESI-TOF, *m/z*) calcd. for C₂₂H₃₀BrN₄O₃ [M+H]⁺ calc.: 477.1496; found: 477.1491.

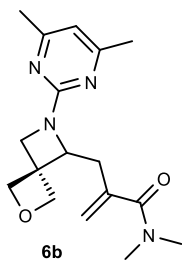
***Trans-5b'*:**

R_f 0.41 (EtOAc:MeOH = 10:1, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.37 (d, *J* = 8.8 Hz, 1H), 5.44 (d, *J* = 1.7 Hz, 2H), 5.28 (d, *J* = 1.4 Hz, 2H), 5.09 (d, *J* = 7.3 Hz, 2H), 4.62 (d, *J* = 7.3 Hz, 2H), 4.49 (dd, *J* = 10.0, 2.7 Hz, 2H), 3.22 (dq, *J* = 15.9, 2.0 Hz, 2H), 3.10 (s, 6H), 2.96 (s, 6H), 2.47 (dd, *J* = 15.9, 10.0 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 171.1, 155.2, 148.9, 141.1, 139.6, 117.8, 109.8, 108.2, 76.8, 64.7, 47.1, 39.0, 35.0, 33.3.

HRMS (ESI-TOF, *m/z*) calcd. for C₂₂H₃₀BrN₄O₃ [M+H]⁺ calc.: 477.1496; found: 477.1485.



Compound 6b.

Prepared following general procedure C, using compound **6** (41 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (37 mg, 0.12 mmol, 58% yield) was isolated as an amorphous white solid, alongside double derivatized products (9 mg, 0.02 mmol, 10% yield).

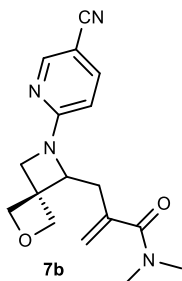
R_f 0.52 (EtOAc:MeOH = 10:1, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 6.31 (s, 1H), 5.43 (s, 1H), 5.29 (s, 1H), 5.11 (d, *J* = 7.1 Hz, 1H), 4.78 (d, *J* = 6.7 Hz, 1H), 4.73 – 4.63 (m, 2H), 4.49 (dd, *J* = 10.1, 3.0 Hz, 1H), 4.23 (d, *J* = 9.3 Hz, 1H), 4.11 (d, *J* = 9.3 Hz, 1H), 3.29 (ddt, *J* = 16.0, 3.2, 1.7 Hz, 1H), 3.10 (s, 3H), 2.96 (s, 3H), 2.71 (ddt, *J* = 16.0, 10.1, 1.2 Hz, 1H), 2.25 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 171.5, 167.3, 163.3, 142.0, 116.9, 110.4, 81.0, 77.5, 66.7, 58.9, 42.7, 38.8, 35.4, 34.9, 24.0.

IR (ATR, neat, cm⁻¹) 1617 (m), 1575 (s), 1558 (s), 1495 (m), 1455 (s), 1382 (m), 1338 (m), 1313 (m), 1118 (m), 975 (m), 789 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₇H₂₅N₄O₂ [M+H]⁺ calc.: 317.1972; found: 317.1967.



Compound 7b.

Prepared following general procedure C, using compound **7** (40 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (26 mg, 0.08 mmol, 42% yield) was isolated as an amorphous white solid, alongside recovered starting material (3 mg, 0.01 mmol, 7% yield), and double derivatized products (18 mg, 0.04 mmol, 21% yield).

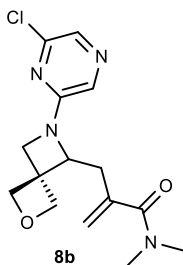
R_f 0.52 (EtOAc:MeOH = 10:1, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.35 (dd, *J* = 2.3, 0.8 Hz, 1H), 7.57 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.45 (dd, *J* = 8.8, 0.8 Hz, 1H), 5.46 (s, 1H), 5.30 (s, 1H), 5.10 (d, *J* = 7.3 Hz, 1H), 4.81 – 4.65 (m, 3H), 4.56 (dd, *J* = 8.6, 4.1 Hz, 1H), 4.30 (dd, *J* = 9.4, 1.1 Hz, 1H), 4.11 (d, *J* = 9.4 Hz, 1H), 3.19 – 2.76 (m, 8H).

¹³C NMR (75 MHz, CDCl₃) δ 171.0, 160.5, 152.9, 140.4, 139.5, 118.8, 118.7, 106.3, 97.5, 81.2, 76.8, 67.6, 59.3, 43.1, 39.0, 36.0, 35.0.

IR (ATR, neat, cm⁻¹) 2933 (w), 2869 (w), 2216 (m), 1613 (m), 1595 (s), 1500 (s), 1417 (m), 1395 (w), 1309 (w), 975 (m).

HRMS (ESI-TOF, m/z) calcd. for C₁₇H₂₁N₄O₂ [M+H]⁺ calc.: 313.1659; found: 313.1661.



Compound 8b.

Prepared following general procedure C, using compound **8** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (31 mg, 0.10 mmol, 48% yield) was isolated as an amorphous white solid, alongside recovered starting material (3 mg, 0.01 mmol, 7% yield), and double derivatized products (13 mg, 0.03 mmol, 15% yield).

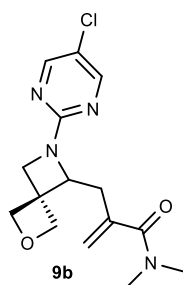
R_f 0.53 (EtOAc:MeOH = 10:1, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 7.85 (s, 1H), 7.75 (s, 1H), 5.45 (s, 1H), 5.31 (s, 1H), 5.12 (d, *J* = 7.3 Hz, 1H), 4.79 (d, *J* = 6.9 Hz, 1H), 4.74 – 4.62 (m, 2H), 4.56 (dd, *J* = 8.6, 4.1 Hz, 1H), 4.32 (dd, *J* = 9.1, 1.1 Hz, 1H), 4.09 (d, *J* = 9.1 Hz, 1H), 3.17 – 2.79 (m, 8H).

¹³C NMR (75 MHz, CDCl₃) δ 171.0, 155.2, 147.1, 140.6, 131.9, 128.2, 118.6, 80.9, 77.0, 67.8, 59.7, 43.7, 38.9, 36.1, 34.9.

IR (ATR, neat, cm⁻¹) 1613 (s), 1563 (s), 1501 (s), 1456 (s), 1407 (s), 1394 (s), 1345 (m), 1317 (w), 1202 (w), 1173 (s), 1104 (s), 989 (m), 974 (s), 943 (m), 834 (m).

HRMS (ESI-TOF, m/z) calcd. for C₁₅H₂₀ClN₄O₂ [M+H]⁺ calc.: 323.1269; found: 323.1268.



Compound 9b.

Prepared following general procedure C, using compound **9** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (44 mg, 0.14 mmol, 68% yield) was isolated as an amorphous white solid, alongside recovered starting material (5 mg, 0.02 mmol, 10% yield), and double derivatized products (18 mg, 0.04 mmol, 21% yield).

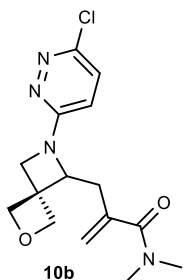
R_f 0.53 (EtOAc:MeOH = 10:1, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.21 (s, 2H), 5.48 – 5.41 (m, 1H), 5.30 (s, 1H), 5.13 (d, *J* = 7.2 Hz, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.75 – 4.64 (m, 2H), 4.53 (dd, *J* = 9.8, 3.4 Hz, 1H), 4.24 (dd, *J* = 9.5, 1.1 Hz, 1H), 4.13 (d, *J* = 9.5 Hz, 1H), 3.22 (ddt, *J* = 16.0, 3.4, 1.7 Hz, 1H), 3.11 (s, 3H), 2.97 (s, 3H), 2.78 (ddt, *J* = 16.1, 9.9, 1.2 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 171.2, 161.1, 156.2, 141.2, 119.9, 117.6, 81.0, 77.2, 67.2, 59.1, 42.9, 39.0, 35.3, 35.0.

IR (ATR, neat, cm⁻¹) 2868 (w), 1639 (m), 1615 (m), 1575 (s), 1525 (s), 1489 (s), 1458 (s), 1389 (m), 1367 (m), 1135 (m), 1124 (m), 975 (m), 789 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₅H₂₀ClN₄O₂ [M+H]⁺ calc.: 323.1269; found: 323.1267.



Compound 10b.

Prepared following general procedure C, using compound **10** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (28 mg, 0.09 mmol, 43% yield) was isolated as an amorphous white solid, alongside recovered starting material (15 mg, 0.07 mmol, 35% yield).

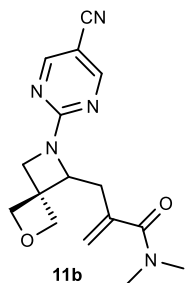
R_f 0.39 (EtOAc:MeOH = 10:1, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 7.17 (d, *J* = 9.3 Hz, 1H), 6.87 (d, *J* = 9.3 Hz, 1H), 5.45 (s, 1H), 5.26 (s, 1H), 5.11 (d, *J* = 7.3 Hz, 1H), 4.81 – 4.67 (m, 3H), 4.56 (dd, *J* = 7.7, 5.0 Hz, 1H), 4.34 (dd, *J* = 9.2, 1.0 Hz, 1H), 4.15 (d, *J* = 9.2 Hz, 1H), 3.16 – 2.81 (m, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 171.2, 160.2, 147.7, 140.4, 128.9, 118.9, 115.6, 81.1, 76.9, 68.1, 59.9, 43.7, 39.0, 36.8, 34.9.

IR (ATR, neat, cm⁻¹) 2933 (w), 2868 (w), 1639 (m), 1611 (s), 1582 (s), 1529 (m), 1434 (s), 1393 (m), 1348 (m), 1153 (m), 975 (m), 758 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₅H₂₀ClN₄O₂ [M+H]⁺ calc.: 323.1269; found: 323.1270.



Compound 11b.

Prepared following general procedure C, using compound **11** (40 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (26 mg, 0.08 mmol, 41% yield) was isolated as an amorphous white solid, alongside double derivatized products (17 mg, 0.04 mmol, 20% yield).

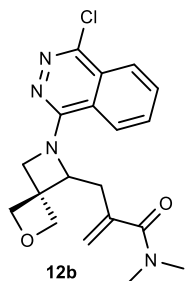
R_f 0.48 (EtOAc:MeOH = 10:1, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.50 (s, 2H), 5.47 (t, *J* = 1.6 Hz, 1H), 5.35 (s, 1H), 5.15 (d, *J* = 7.3 Hz, 1H), 4.88 – 4.76 (m, 2H), 4.75 – 4.66 (m, 2H), 4.39 – 4.25 (m, 2H), 3.28 (ddt, *J* = 16.0, 3.4, 1.7 Hz, 1H), 3.13 (s, 3H), 2.98 (s, 3H), 2.82 (ddt, *J* = 16.0, 9.8, 1.2 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 170.9, 161.0, 160.9, 140.7, 117.9, 116.6, 97.0, 81.0, 77.4, 67.5, 58.8, 42.9, 39.0, 35.0, 34.5.

IR (ATR, neat, cm⁻¹) 2938 (w), 2873 (w), 2220 (m), 1615 (m), 1595 (s), 1541 (m), 1513 (m), 1399 (m), 1227 (w), 1125 (w), 975 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₆H₂₀N₅O₂ [M+H]⁺ calc.: 314.1612; found: 314.1609.



Compound 12b.

Prepared following general procedure C, using compound **12** (52 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (34 mg, 0.09 mmol, 46% yield) was isolated as an amorphous white solid, alongside recovered starting material (3 mg, 0.01 mmol, 6% yield), and double derivatized products (17 mg, 0.04 mmol, 18% yield).

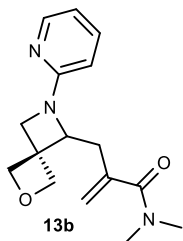
R_f 0.47 (EtOAc:MeOH = 10:1, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.24 – 8.13 (m, 1H), 7.94 – 7.77 (m, 3H), 5.47 (td, *J* = 1.5, 0.7 Hz, 1H), 5.34 – 5.23 (m, 2H), 5.09 (dd, *J* = 8.4, 4.2 Hz, 1H), 4.96 – 4.82 (m, 2H), 4.76 (dd, *J* = 7.3, 0.7 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.34 (d, *J* = 8.3 Hz, 1H), 3.16 – 2.93 (m, 5H), 2.84 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 171.4, 157.2, 147.9, 141.6, 132.7, 132.1, 127.0, 125.8, 124.0, 121.2, 117.9, 80.9, 77.5, 67.4, 64.8, 44.0, 39.0, 35.1, 34.9.

IR (ATR, neat, cm⁻¹) 2359 (s), 2329 (s), 1614 (m), 1494 (m), 1419 (m), 1348 (m), 1295 (w), 1120 (w), 974 (m).

HRMS (ESI-TOF, m/z) calcd. for C₁₉H₂₂ClN₄O₂ [M+H]⁺ calc.: 373.1426; found: 373.1427.



Compound 13b.

Prepared following general procedure C, using compound **13** (35 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (32 mg, 0.11 mmol, 56% yield) was isolated as a colorless oil, alongside recovered starting material (3 mg, 0.02 mmol, 9% yield), and double derivatized products (28 mg, 0.07 mmol, 35% yield).

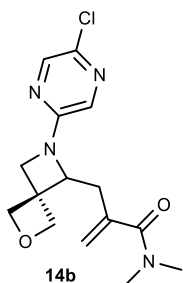
R_f 0.47 (EtOAc:MeOH = 10:1, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.11 (ddd, *J* = 5.1, 2.0, 0.9 Hz, 1H), 7.50 – 7.38 (m, 1H), 6.62 (ddd, *J* = 7.2, 5.0, 1.0 Hz, 1H), 6.45 (d, *J* = 8.4 Hz, 1H), 5.50 (s, 1H), 5.30 (s, 1H), 5.14 (d, *J* = 7.2 Hz, 1H), 4.76 – 4.65 (m, 3H), 4.39 (dd, *J* = 9.2, 3.6 Hz, 1H), 4.24 (d, *J* = 8.8 Hz, 1H), 4.01 (d, *J* = 8.8 Hz, 1H), 3.20 – 3.06 (m, 4H), 2.95 (s, 3H), 2.82 (dd, *J* = 15.6, 9.2 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 171.3, 160.4, 147.9, 141.0, 137.4, 118.2, 113.8, 107.1, 81.1, 77.4, 67.2, 59.7, 43.1, 39.1, 36.6, 35.0.

IR (ATR, neat, cm⁻¹) 2929 (w), 2865 (w), 1639 (m), 1613 (s), 1591 (s), 1560 (w), 1481 (s), 1436 (s), 1392 (m), 1123 (w), 975 (m).

HRMS (ESI-TOF, m/z) calcd. for C₁₆H₂₂N₃O₂ [M+H]⁺ calc.: 288.1707; found: 288.1701.



Compound 14b.

Prepared following general procedure C, using compound **14** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired

product (25 mg, 0.08 mmol, 39% yield) was isolated as an amorphous white solid, alongside recovered starting material (10 mg, 0.05 mmol, 24% yield), and double derivatized products (10 mg, 0.02 mmol, 12% yield).

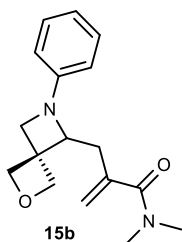
R_f 0.59 (EtOAc:MeOH = 10:1, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.00 (d, *J* = 1.4 Hz, 1H), 7.66 (d, *J* = 1.4 Hz, 1H), 5.47 (t, *J* = 1.5 Hz, 1H), 5.30 (d, *J* = 1.2 Hz, 1H), 5.12 (d, *J* = 7.3 Hz, 1H), 4.81 – 4.66 (m, 3H), 4.53 (dd, *J* = 8.7, 4.3 Hz, 1H), 4.28 (d, *J* = 9.0 Hz, 1H), 4.03 (d, *J* = 8.9 Hz, 1H), 3.13 – 2.93 (m, 7H), 2.83 (ddd, *J* = 15.3, 8.7, 1.4 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 171.0, 154.9, 141.4, 140.4, 137.5, 129.5, 118.6, 80.8, 77.1, 67.9, 59.8, 43.7, 39.0, 36.0, 35.0.

IR (ATR, neat, cm⁻¹) 2931 (w), 2869 (w), 2308 (w), 1738 (w), 1615 (s), 1567 (s), 1511 (m), 1473 (s), 1392 (m), 1345 (m), 1210 (w), 1171 (w), 1126 (m), 975 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₅H₂₀ClN₄O₂ [M+H]⁺ calc.: 323.1269; found: 323.1270.



Compound 15b.

Prepared following general procedure C, using compound **15** (35 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (20 mg, 0.07 mmol, 35% yield) was isolated as an amorphous

white solid, alongside double derivatized products (19 mg, 0.05 mmol, 24% yield).

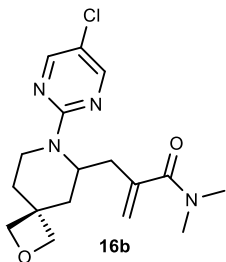
R_f 0.30 (*c*-hexane/EtOAc = 1:2, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 7.27 – 7.15 (m, 2H), 6.77 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.62 – 6.51 (m, 2H), 5.54 (s, 1H), 5.35 – 5.28 (m, 1H), 5.16 (d, *J* = 7.1 Hz, 1H), 4.73 (d, *J* = 7.1 Hz, 1H), 4.66 (s, 2H), 4.25 – 4.10 (m, 2H), 3.74 (d, *J* = 8.0 Hz, 1H), 3.20 – 2.93 (m, 7H), 2.77 (ddd, *J* = 15.6, 9.8, 1.2 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 171.2, 151.1, 140.7, 129.2, 118.6, 118.4, 112.5, 80.8, 68.0, 61.4, 43.1, 39.1, 37.1, 35.1.

IR (ATR, neat, cm⁻¹) 2927 (w), 2864 (w), 1640 (m), 1613 (s), 1598 (s), 1496 (s), 1455 (w), 1392 (m), 1324 (m), 1123 (m), 974 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₇H₂₃N₂O₂ [M+H]⁺ calc.: 287.1754; found: 287.1751.



Compound 16b.

Prepared following general procedure C, using compound **16** (48 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (31 mg, 0.09 mmol, 44% yield) was isolated as an amorphous white solid, alongside recovered starting material (16 mg, 0.07 mmol, 33% yield).

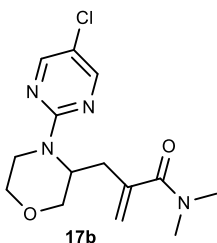
R_f 0.20 (*c*-hexane/EtOAc = 1:2, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 2H), 5.33 (s, 1H), 5.18 – 5.08 (m, 2H), 4.75 (d, *J* = 5.7 Hz, 1H), 4.67 – 4.52 (m, 2H), 4.44 (d, *J* = 5.7 Hz, 1H), 4.21 (d, *J* = 5.7 Hz, 1H), 3.11 – 2.89 (m, 2H), 2.81 (d, *J* = 55.0 Hz, 6H), 2.57 – 2.43 (m, 2H), 2.26 (dq, *J* = 13.3, 2.4 Hz, 1H), 2.16 (dt, *J* = 13.8, 1.9 Hz, 1H), 1.59 (ddd, *J* = 24.0, 13.4, 5.3 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 170.9, 159.8, 156.0, 141.4, 118.1, 118.0, 83.2, 82.4, 49.6, 39.0, 38.0, 36.4, 35.9, 35.7, 35.0, 34.5.

IR (ATR, neat, cm⁻¹) 2928 (w), 2853 (w), 1615 (m), 1582 (s), 1491 (s), 1399 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₇H₂₃ClN₄NaO₂ [M+Na]⁺ calc.: 373.1402; found: 373.1394.



Compound 17b.

Prepared following general procedure C, using compound **17** (40 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (41 mg, 0.13 mmol, 66% yield) was isolated as a colorless oil, alongside recovered starting material (8 mg, 0.04 mmol, 20% yield), and double derivatized products (12 mg, 0.03 mmol, 14% yield).

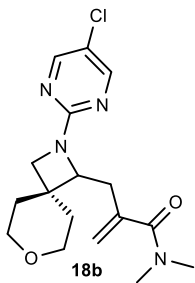
R_f 0.43 (*c*-hexane/EtOAc = 1:2, UV, KMnO₄).

¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 2H), 5.37 (s, 1H), 5.16 (s, 1H), 4.83 – 4.74 (m, 1H), 4.34 (dd, *J* = 13.7, 2.9 Hz, 1H), 4.02 – 3.87 (m, 2H), 3.60 – 3.44 (m, 2H), 3.28 (ddd, *J* = 13.8, 12.3, 3.7 Hz, 1H), 2.99 – 2.75 (m, 7H), 2.68 (dd, *J* = 14.0, 6.9 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 171.2, 159.5, 156.0, 141.6, 118.4, 118.4, 68.3, 67.0, 50.0, 39.7, 38.8, 34.9, 33.2.

IR (ATR, neat, cm^{-1}) 1614 (m), 1580 (s), 1526 (8m), 1478 (s), 1448 (s), 1393 (m), 1229 (m), 1124 (m), 1018 (m), 951 (m), 785 (m).

HRMS (ESI-TOF, m/z) calcd. for $\text{C}_{14}\text{H}_{20}\text{ClN}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ calc.: 311.1269; found: 311.1265.



Compound 18b.

Prepared following general procedure C, using compound **18** (48 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (40 mg, 0.11 mmol, 57% yield) was isolated as an amorphous white solid, alongside recovered starting material (13 mg, 0.06 mmol, 27% yield), and double derivatized products (11 mg, 0.02 mmol, 12% yield).

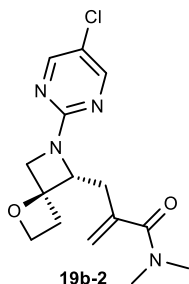
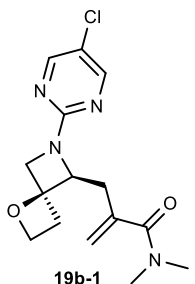
R_f 0.63 (EtOAc:MeOH = 10:1, UV, KMnO_4).

¹H NMR (400 MHz, CDCl_3) δ 8.21 (s, 2H), 5.29 (s, 1H), 5.19 (s, 1H), 4.20 (dd, $J = 10.2, 3.7$ Hz, 1H), 3.99 – 3.76 (m, 5H), 3.37 (tdd, $J = 11.9, 6.4, 2.3$ Hz, 2H), 3.19 – 3.06 (m, 4H), 2.99 (s, 3H), 2.74 (dd, $J = 15.8, 10.2$ Hz, 1H), 2.03 – 1.89 (m, 2H), 1.84 (dq, $J = 13.2, 2.4$ Hz, 1H), 1.64 (dq, $J = 13.3, 2.3$ Hz, 1H).

¹³C NMR (101 MHz, CDCl_3) δ 171.4, 161.5, 156.1, 142.3, 119.5, 116.8, 69.3, 64.9, 64.7, 58.8, 39.0, 37.6, 37.4, 35.0, 33.4, 31.7.

IR (ATR, neat, cm^{-1}) 2931 (w), 2843 (w), 1737 (w), 1641 (m), 1621 (m), 1577 (s), 1526 (m), 1496 (s), 1469 (s), 1388 (w), 1106 (m).

HRMS (ESI-TOF, m/z) calcd. for $\text{C}_{17}\text{H}_{24}\text{ClN}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ calc.: 351.1582; found: 351.1584.



Compounds 19b-1 and 19b-2.

Prepared following general procedure C, using compound **19** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired products (31 mg, 0.10 mmol, 48% yield) were isolated as an inseparable mixture of the two diastereomers in a 10:1 ratio as a colorless oil, alongside recovered starting material (9 mg, 0.04 mmol, 20% yield), and double derivatized products (10 mg, 0.02 mmol, 12% yield).

Note: because of the overlapping signals, especially as regards the ^1H NMR, a precise assignment of the peaks of the minor diastereomer was not feasible.

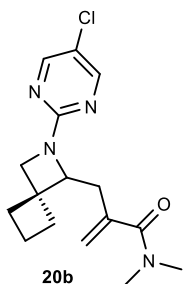
R_f 0.63 (EtOAc:MeOH = 10:1, UV, KMnO₄).

^1H NMR (400 MHz, CDCl₃) **major:** δ 8.19 (s, 2H), 5.42 (s, 1H), 5.27 (s, 1H), 4.60 (ddd, J = 10.1, 3.7, 1.5 Hz, 1H), 4.55 – 4.44 (m, 2H), 4.26 – 4.10 (m, 2H), 3.18 – 2.96 (m, 8H), 2.93 – 2.74 (m, 2H).

^{13}C NMR (101 MHz, CDCl₃) **major:** δ 171.8, 160.8, 156.1, 142.4, 119.5, 117.2, 85.1, 72.5, 67.3, 63.4, 38.8, 34.9, 33.3, 31.3.

IR (ATR, neat, cm⁻¹) 1618 (m), 1574 (s), 1525 (m), 1488 (s), 1449 (s), 1388 (m), 1242 (w), 1143 (m), 976 (m), 952 (m), 789 (m).

HRMS (ESI-TOF, m/z) calcd. for C₁₅H₂₀ClN₄O₂ [M+H]⁺ calc.: 323.1269; found: 323.1264.



Compound 20b.

Prepared following general procedure C, using compound **20** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (0% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (37 mg, 0.12 mmol, 58% yield) was isolated as a colorless oil,

alongside double derivatized products (23 mg, 0.05 mmol, 27% yield).

R_f 0.57 (*c*-hexane/EtOAc = 1:2, UV, KMnO₄).

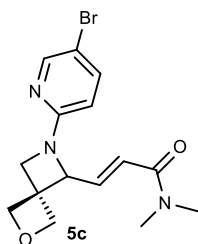
^1H NMR (400 MHz, CDCl₃) δ 8.18 (s, 2H), 5.34 (s, 1H), 5.23 (s, 1H), 4.31 (dd, J = 9.8, 3.5 Hz, 1H), 4.07 (dd, J = 8.8, 1.0 Hz, 1H), 3.97 (d, J = 8.8 Hz, 1H), 3.13 – 3.02 (m, 4H), 2.98 (s, 3H), 2.69 (ddt, J = 15.8, 9.7, 1.1 Hz, 1H), 2.56 – 2.44 (m, 1H), 2.23 (dt, J = 11.3, 8.5 Hz, 1H), 2.08 (ddt, J = 11.9, 8.5, 4.2 Hz, 1H), 1.97 (dtd, J = 14.5, 9.3, 5.2 Hz, 1H), 1.92 – 1.76 (m, 2H).

^{13}C NMR (101 MHz, CDCl₃) δ 171.6, 161.1, 156.0, 142.4, 119.1, 116.6, 68.7, 62.6, 42.8, 38.9, 35.1, 35.0, 33.5, 28.6, 16.4.

IR (ATR, neat, cm⁻¹) 2930 (w), 1640 (m), 1619 (m), 1574 (s), 1523 (m), 1488 (s), 1460 (s), 1388 (m), 1366 (m), 1296 (w), 1122 (m), 977 (w), 786 (m).

HRMS (ESI-TOF, m/z) calcd. for C₁₆H₂₂ClN₄O [M+H]⁺ calc.: 321.1477; found: 321.1473.

HAT vinylation products



Compound 5c.

Prepared following general procedure D, using compound **5** (51 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (25 mg, 0.07 mmol, 35% yield) was isolated as an amorphous white solid, alongside recovered starting material (18 mg, 0.07 mmol, 35% yield).

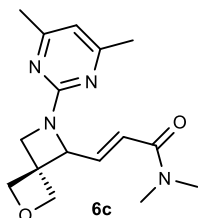
R_f 0.47 (EtOAc:MeOH = 10:1, UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃) δ 8.17 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.09 (dd, *J* = 15.0, 5.2 Hz, 1H), 6.58 (dd, *J* = 15.0, 1.5 Hz, 1H), 6.23 (dd, *J* = 8.8, 0.7 Hz, 1H), 4.87 (d, *J* = 7.2 Hz, 1H), 4.79 – 4.62 (m, 5H), 4.21 (dd, *J* = 8.9, 1.2 Hz, 1H), 4.09 (d, *J* = 8.9 Hz, 1H), 3.04 (s, 3H), 3.02 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 165.7, 158.8, 148.9, 140.5, 139.9, 123.1, 109.3, 108.5, 80.0, 77.8, 70.2, 59.0, 44.2, 37.6, 35.9.

IR (ATR, neat, cm⁻¹) 2866 (w), 1660 (m), 1615 (m), 1579 (s), 1547 (w), 1462 (s), 1391 (s), 1343 (m), 1292 (w), 1148 (m), 1091 (w), 974 (m).

HRMS (ESI-TOF, *m/z*) calcd. for C₁₅H₁₉BrN₃O₂ [M+H]⁺ calc.: 352.0655; found: 352.0645.



Compound 6c.

Prepared following general procedure D, using compound **6** (42 mg, 0.20 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (37 mg, 0.12 mmol, 58% yield) was isolated as an amorphous white solid, alongside double derivatized products (23 mg, 0.05 mmol, 27% yield).

R_f 0.31 (EtOAc:MeOH = 10:1, UV, KMnO₄).

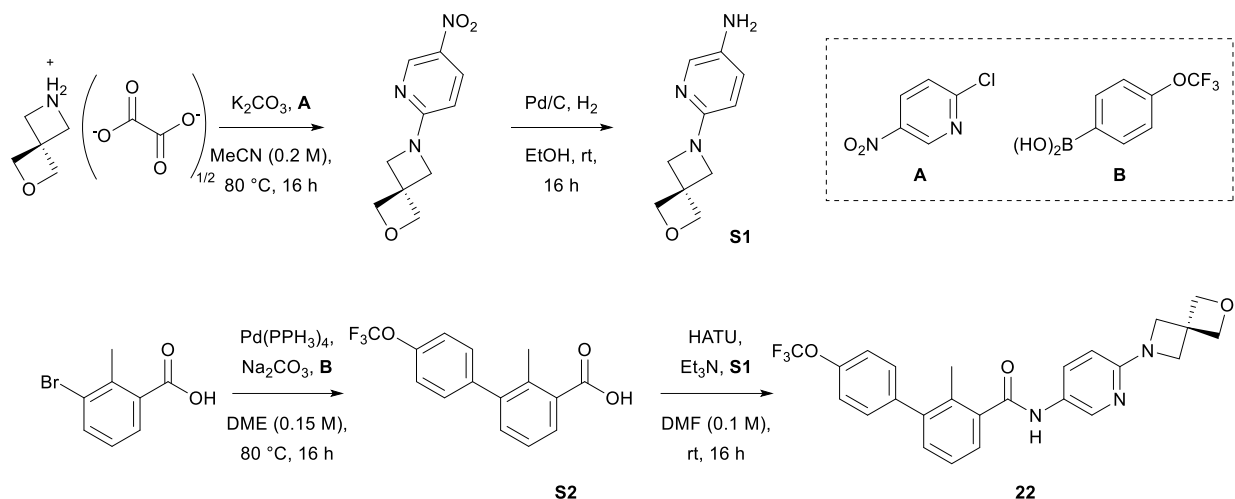
¹H NMR ¹H NMR (300 MHz, CDCl₃) δ 7.01 (dd, *J* = 15.0, 5.3 Hz, 1H), 6.58 (dd, *J* = 15.0, 1.6 Hz, 1H), 6.37 (s, 1H), 4.91 (t, *J* = 6.6 Hz, 2H), 4.78 (q, *J* = 7.0 Hz, 2H), 4.63 (d, *J* = 7.2 Hz, 1H), 4.33 – 4.16 (m, 2H), 3.02 (d, *J* = 10.1 Hz, 6H), 2.27 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 167.5, 166.4, 163.3, 140.6, 123.0, 111.0, 80.7, 77.8, 69.3, 58.9, 43.5, 37.5, 35.8, 24.0.

IR (ATR, neat, cm⁻¹) 2868 (w), 1662 (m), 1618 (m), 1578 (s), 1455 (s), 1382 (m), 1335 (m), 1299 (w), 1149 (w), 974 (m).

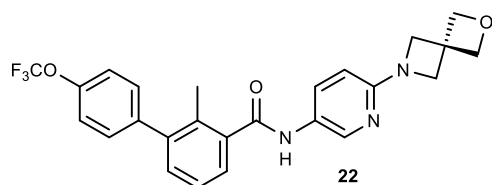
HRMS (ESI-TOF, m/z) calcd. for C₁₆H₂₃N₄O₂ [M+H]⁺ calc.: 303.1816; found: 303.1814.

Synthesis and derivatization of sonidegib analogue



Compounds S1 and S2.

Compounds **S1**⁹ and **S2**¹⁰ were synthesized according to reported literature procedures.



Compound 22.

Aminopyridine **S1** (165 mg, 0.86 mmol, 1 eq) and carboxylic acid **S2** (256 mg, 0.86 mmol, 1 eq) were weighted in an over dried round-bottom flask. DMF (8.6 mL, 0.1 M) was added, followed by

triethylamine (105 mg, 145 μ L, 1.04 mmol, 1.2 eq), and HATU (329 mg, 0.86 mmol, 1 eq). The mixture was stirred at room temperature for 16 h. After completion, most of the DMF was removed *via* rotary evaporation, and the crude dissolved in the remaining DMF was directly purified with reverse-phase column chromatography using a water/acetonitrile mixture as eluent (5% to 95% acetonitrile). The desired product (182 mg, 0.39 mmol, 45% yield) was isolated as an amorphous white solid.

Note: because of coupling with fluorine, the trifluoromethyl carbon signals are clearly visible only as regards the two central peaks of the quartet at 121.9 and 119.4 ppm.

R_f 0.13 (*c*-hexane/EtOAc = 1:2, UV, KMnO₄).

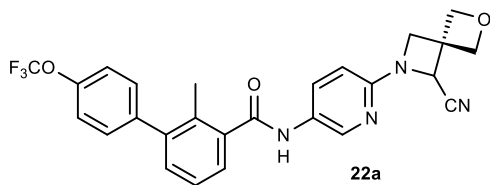
¹H NMR (400 MHz, CDCl₃) δ 8.15 (d, *J* = 2.6 Hz, 1H), 8.04 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.37 – 7.24 (m, 5H), 6.35 (d, *J* = 8.9 Hz, 1H), 4.85 (s, 4H), 4.17 (s, 4H), 2.32 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 168.7, 158.0, 148.6, 142.4, 140.5, 140.0, 137.7, 133.6, 131.8, 131.7, 130.7, 126.2, 126.0, 125.9, 121.9, 120.9, 119.4, 106.3, 81.4, 60.6, 39.1, 17.8.

¹⁹F NMR (377 MHz, CDCl₃) δ -57.78.

IR (ATR, neat, cm⁻¹) 1646 (m), 1505 (m), 1306 (s), 1163 (m).

HRMS (ESI-TOF, m/z) calcd. for C₂₅H₂₃F₃N₃O₃ [M+H]⁺ calc.: 470.1686; found: 470.1687.



Compound 22a.

Prepared following general procedure B, using compound **22** (47 mg, 0.10 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate mixture as eluent (10% to 100% ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (23 mg, 0.05 mmol, 47% yield) was isolated as an amorphous white solid.

Note: because of coupling with fluorine, the trifluoromethyl carbon signals are clearly visible only as regards three peaks of the quartet at 124.5, 121.9, and 119.4 ppm.

R_f 0.47 (c-hexane:EtOAc = 1:2, UV, KMnO₄).

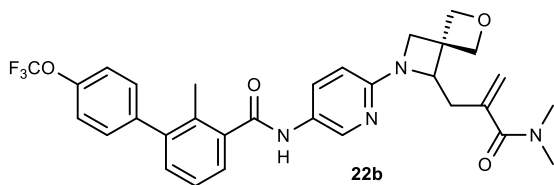
¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, *J* = 2.6 Hz, 1H), 8.16 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.55 – 7.43 (m, 2H), 7.36 – 7.24 (m, 5H), 6.50 (d, *J* = 8.8 Hz, 1H), 5.19 (d, *J* = 7.7 Hz, 1H), 4.96 – 4.89 (m, 2H), 4.82 (s, 2H), 4.29 (d, *J* = 8.1 Hz, 1H), 4.09 (d, *J* = 8.1 Hz, 1H), 2.32 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 168.8, 155.4, 148.7, 142.5, 140.4, 139.9, 137.5, 133.7, 132.0, 131.5, 130.7, 128.1, 126.1, 126.1, 124.5, 121.9, 120.9, 119.4, 116.0, 107.0, 79.0, 78.3, 59.5, 57.8, 42.0, 17.8.

¹⁹F NMR (377 MHz, CDCl₃) δ -57.78.

IR (ATR, neat, cm⁻¹) 2874 (w), 1653 (w), 1609 (w), 1493 (s), 1389 (w), 1255 (s), 1219 (m), 1163 (m).

HRMS (ESI-TOF, m/z) calcd. for C₂₆H₂₂F₃N₄O₃ [M+H]⁺ calc.: 495.1639; found: 495.1633.



Compound 22b.

Prepared following general procedure C, using compound **22** (48 mg, 0.10 mmol, 1 eq). The crude was purified using a cyclohexane/ethyl acetate/methanol mixture as eluent (10% to 100% ethyl acetate in cyclohexane, then 0% to 20% methanol in ethyl acetate) for normal phase, and a water/acetonitrile mixture as eluent for reverse phase (5% to 95% acetonitrile). The desired product (16 mg, 0.03 mmol, 28% yield) was isolated as an amorphous white solid.

Note: because of rotamerism, one quaternary and one non-quaternary aromatic carbons do not present intensities high enough to be detected in the ^{13}C NMR spectrum. This phenomenon can be clearly seen through comparison of the ^{13}C aromatic region of the starting material with the product one since the chemical shifts of the aromatic moieties are largely unaffected by the transformation.

R_f 0.56 (EtOAc:MeOH = 10:1, UV, KMnO₄).

^1H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H), 8.05 (s, 1H), 7.50 (dd, J = 6.7, 2.4 Hz, 1H), 7.35 – 7.23 (m, 5H), 6.53 (d, J = 8.9 Hz, 1H), 5.49 (s, 1H), 5.28 (s, 1H), 5.11 (d, J = 7.3 Hz, 1H), 4.71 (dd, J = 7.0, 4.0 Hz, 3H), 4.44 (dd, J = 8.7, 4.6 Hz, 1H), 4.28 (d, J = 8.8 Hz, 2H), 4.02 (d, J = 8.8 Hz, 1H), 3.20 – 2.91 (m, 7H), 2.81 (dd, J = 15.3, 8.4 Hz, 1H).

^{13}C NMR (101 MHz, CDCl₃) δ 171.4, 168.9, 148.6, 142.3, 140.4, 140.1, 137.6, 133.7, 132.3, 131.8, 130.8, 126.6, 126.4, 126.0, 124.5, 121.9, 120.9, 119.4, 118.6, 116.8, 107.5, 81.0, 77.4, 67.7, 60.1, 43.1, 39.1, 37.0, 35.1, 17.8.

^{19}F NMR (377 MHz, CDCl₃) δ -57.77.

IR (ATR, neat, cm⁻¹) 1611 (m), 1493 (s), 1392 (m), 1256 (s), 733 (m).

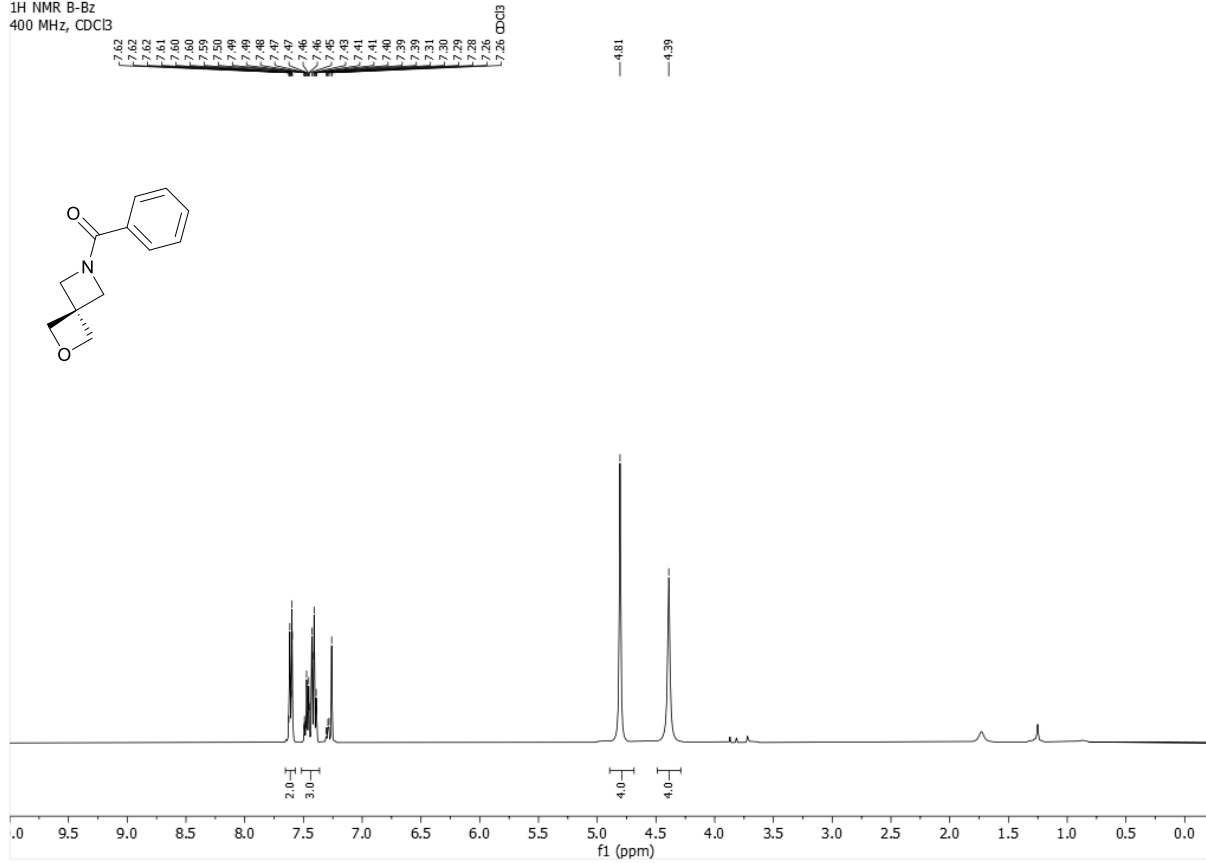
HRMS (ESI-TOF, m/z) calcd. for C₃₁H₃₂F₃N₄O₄ [M+H]⁺ calc.: 581.2370; found: 581.2359.

References

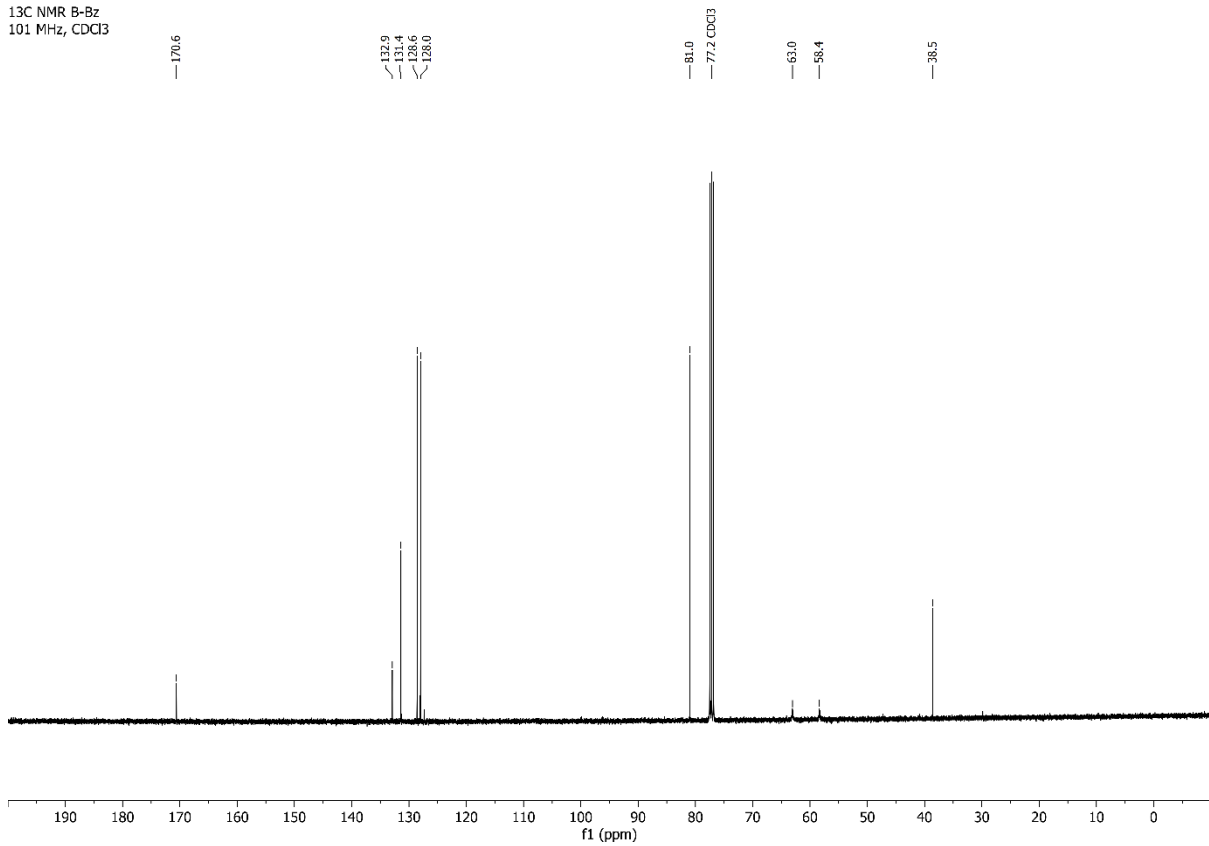
1. Timothy J. Fazekas et al., Diversification of aliphatic C–H bonds in small molecules and polyolefins through radical chain transfer, *Science*, 2022, **375**, 545-550.
2. V. Gembus, S. Postikova, V. Levacher, and J.-F. Brière, Highly Regio- and Diastereoselective Anionic [3+2] Cycloaddition under Phase Transfer Catalytic Conditions, *J. Org. Chem.*, 2011, **76**, 4194–4199.
3. K. Kiyokawa, T. Nagata, J. Hayakawa, and S. Minakata, Straightforward Synthesis of 1,2-Dicyanoalkanes from Nitroalkenes and Silyl Cyanide Mediated by Tetrabutylammonium Fluoride, *Chem. Eur. J.*, 2015, **21**, 1280 – 1285.
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6. J. A. Burkhard, New opportunities for four-membered heterocycles from synthetic studies to unique applications in drug discovery, Doctoral Thesis, 2011, ETH, Zurich.vt
7. C. Ungarean, E. Larin, D. Egger et al., The Reactivity and Selectivity of Azaspirocycles in Radical C–H Functionalization, *Org. Lett.* in press.
8. A. Ruffoni, F. Juliá, T. D. Svejstrup et al., Practical and regioselective amination of arenes using alkyl amines, *Nat. Chem.*, 2019, **11**, 426–433.
9. Patent WO 2015/143380 A1.
10. S. Pan et al., Discovery of NVP-LDE225, a Potent and Selective Smoothed Antagonist, *ACS Med. Chem. Lett.*, 2010, **3**, 130–134.

NMR spectra

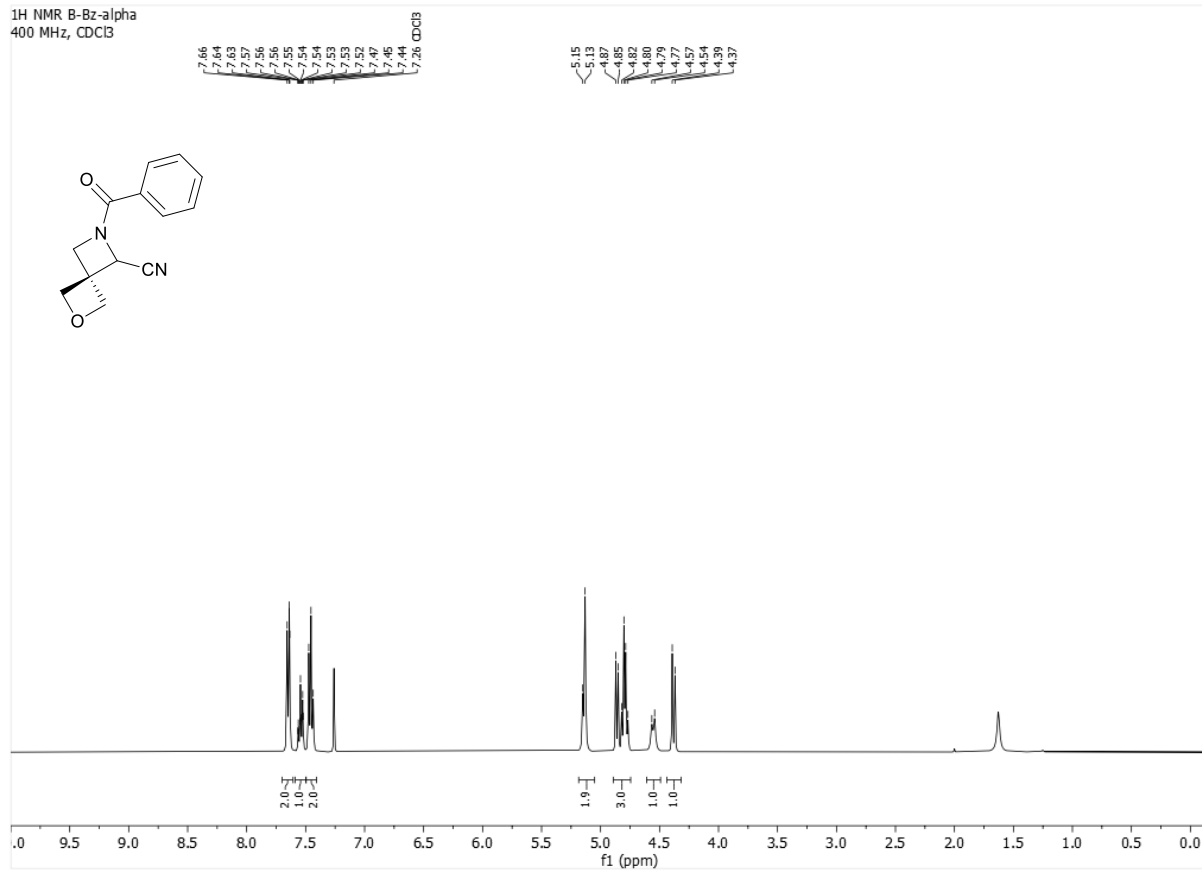
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400 MHz, CDCl₃



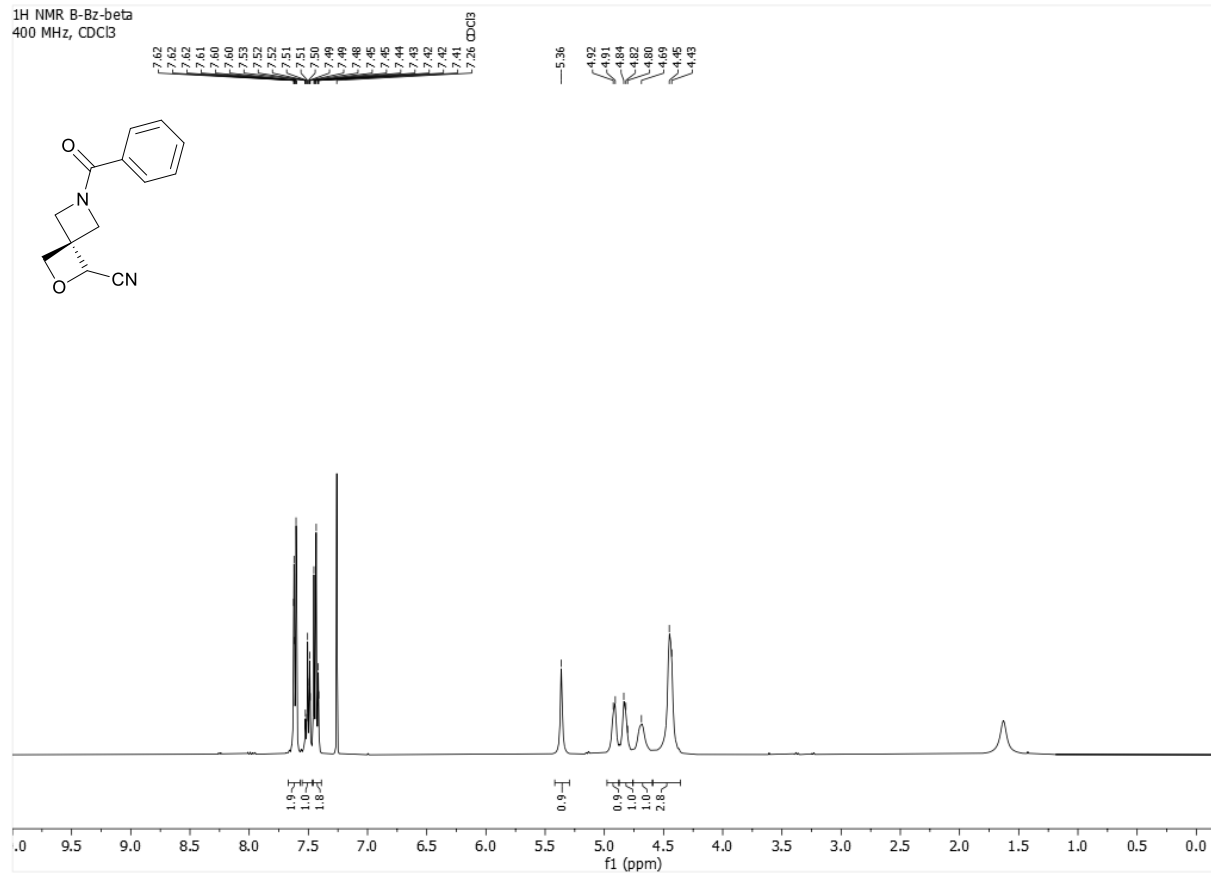
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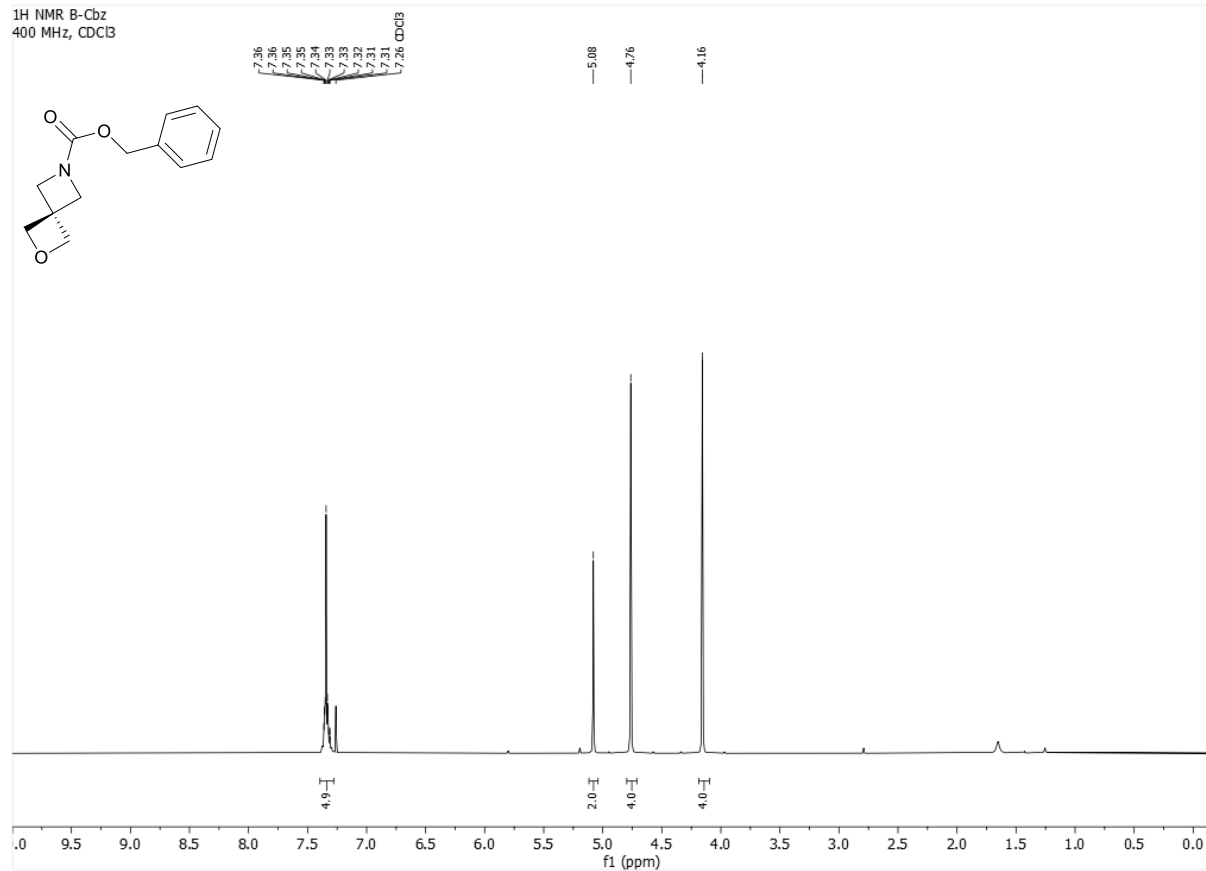
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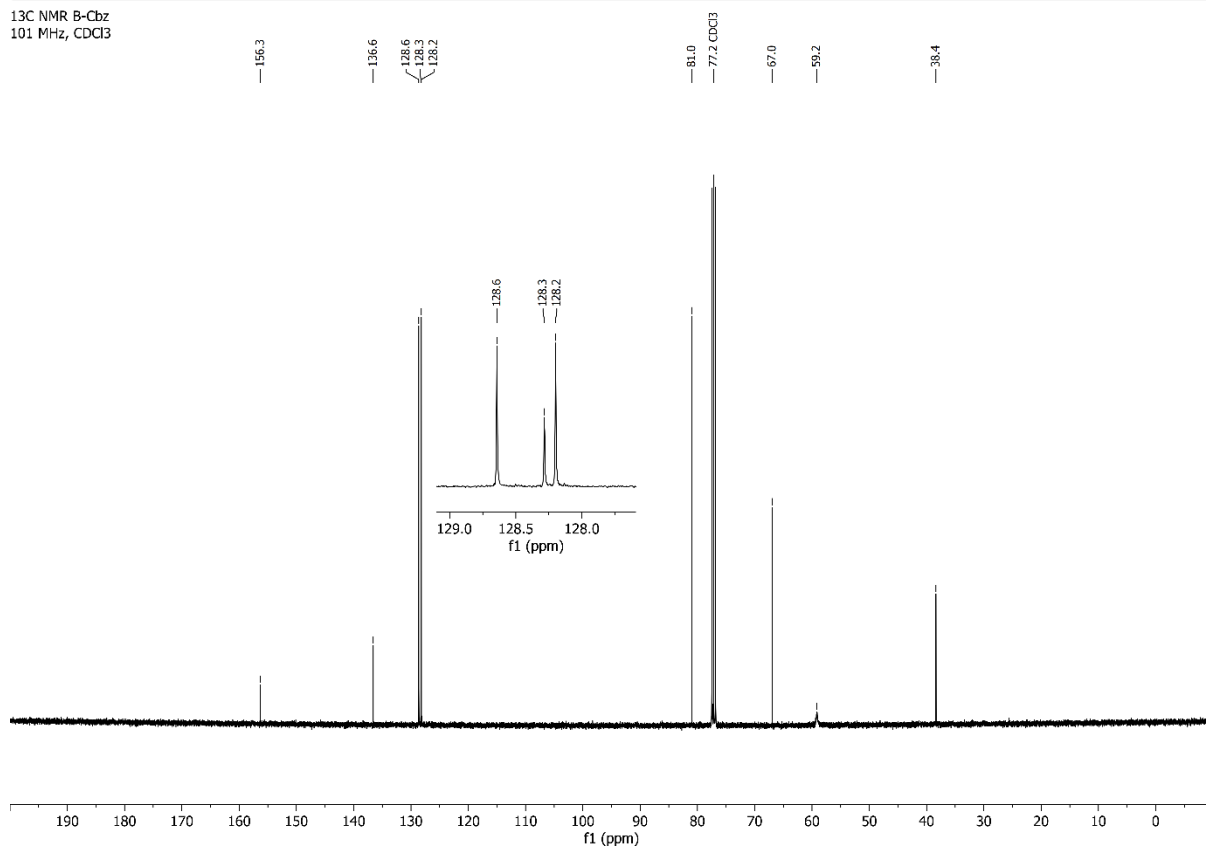
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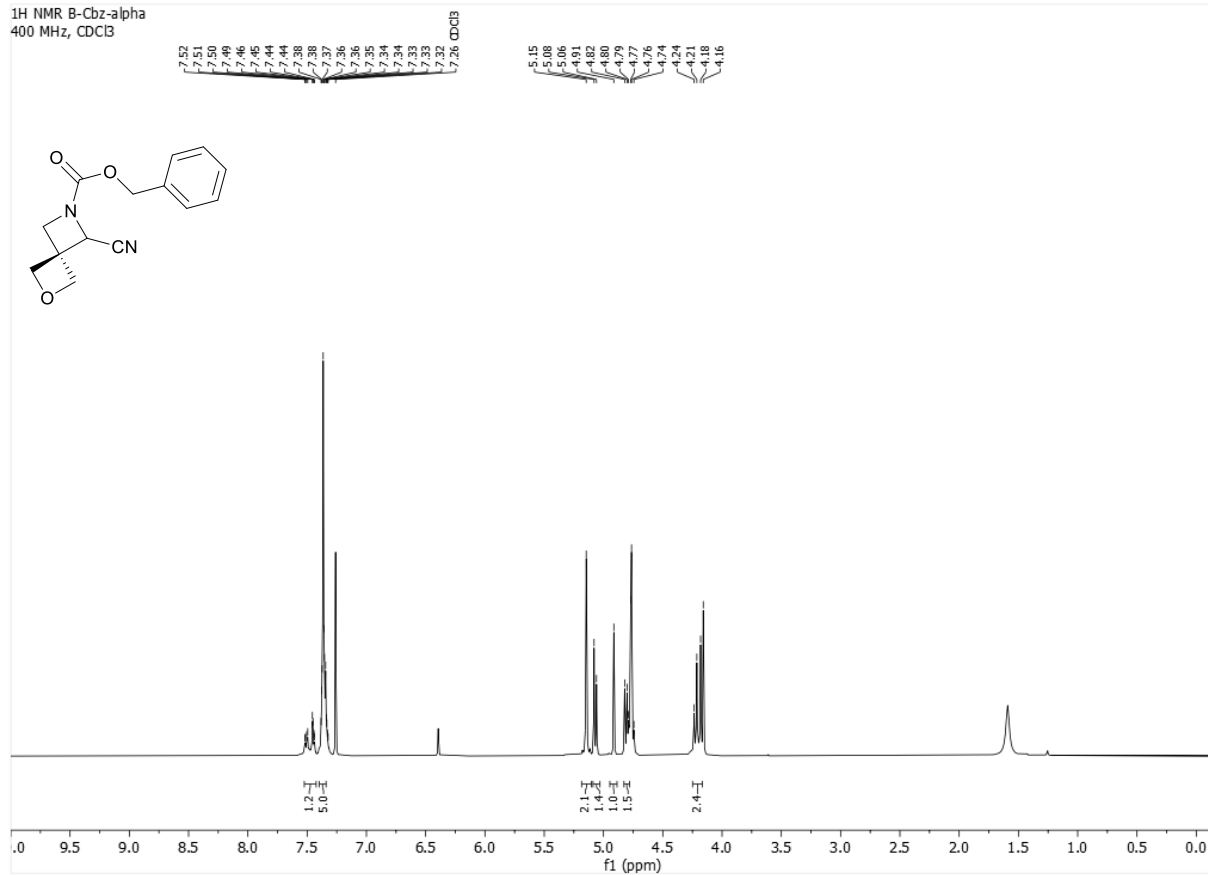
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¹³C NMR B-Cbz
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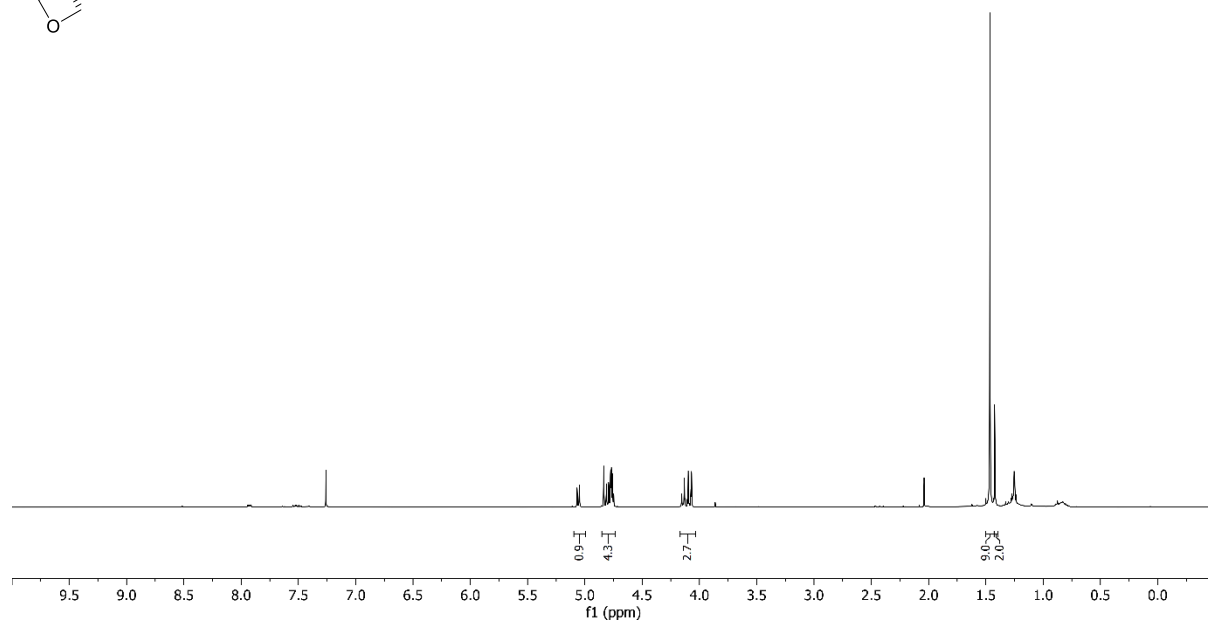
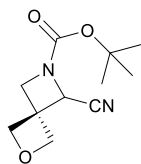


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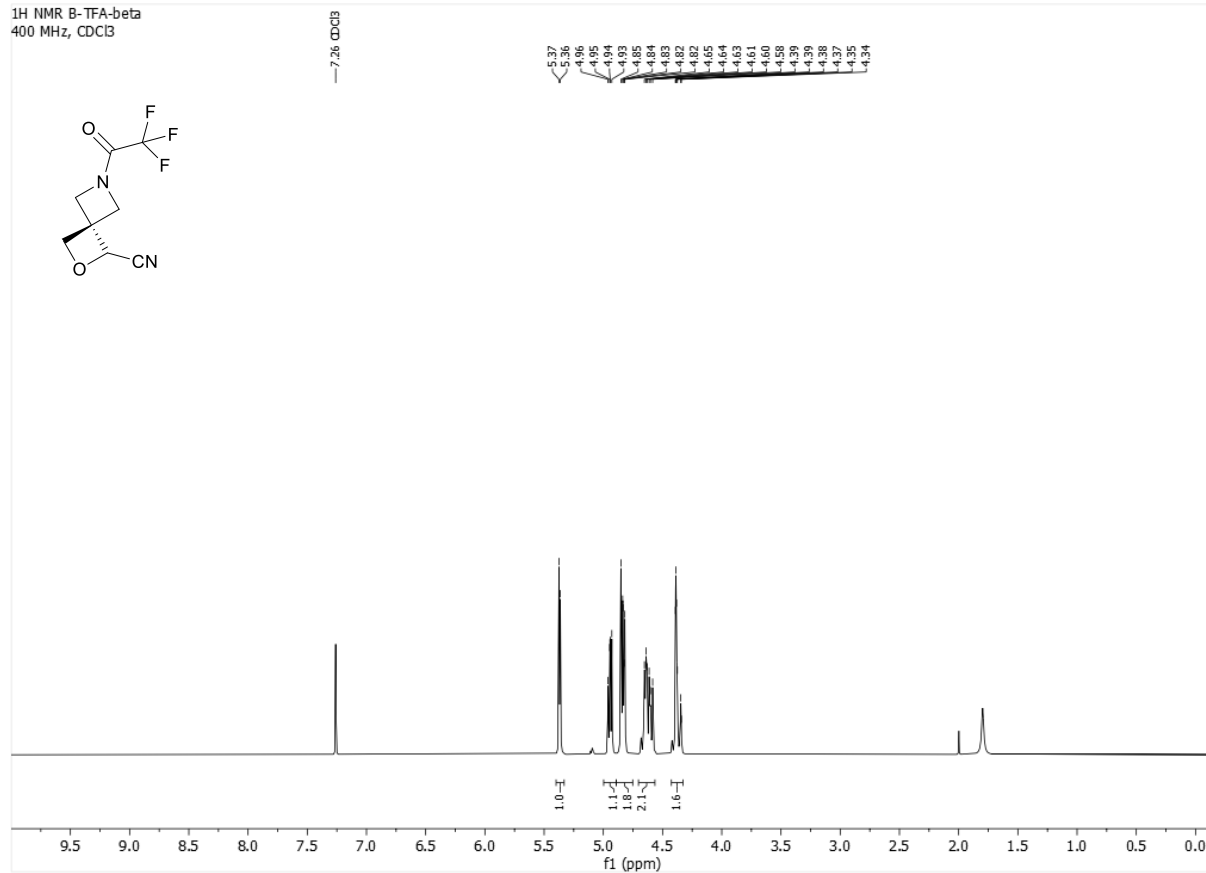
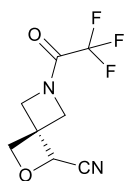


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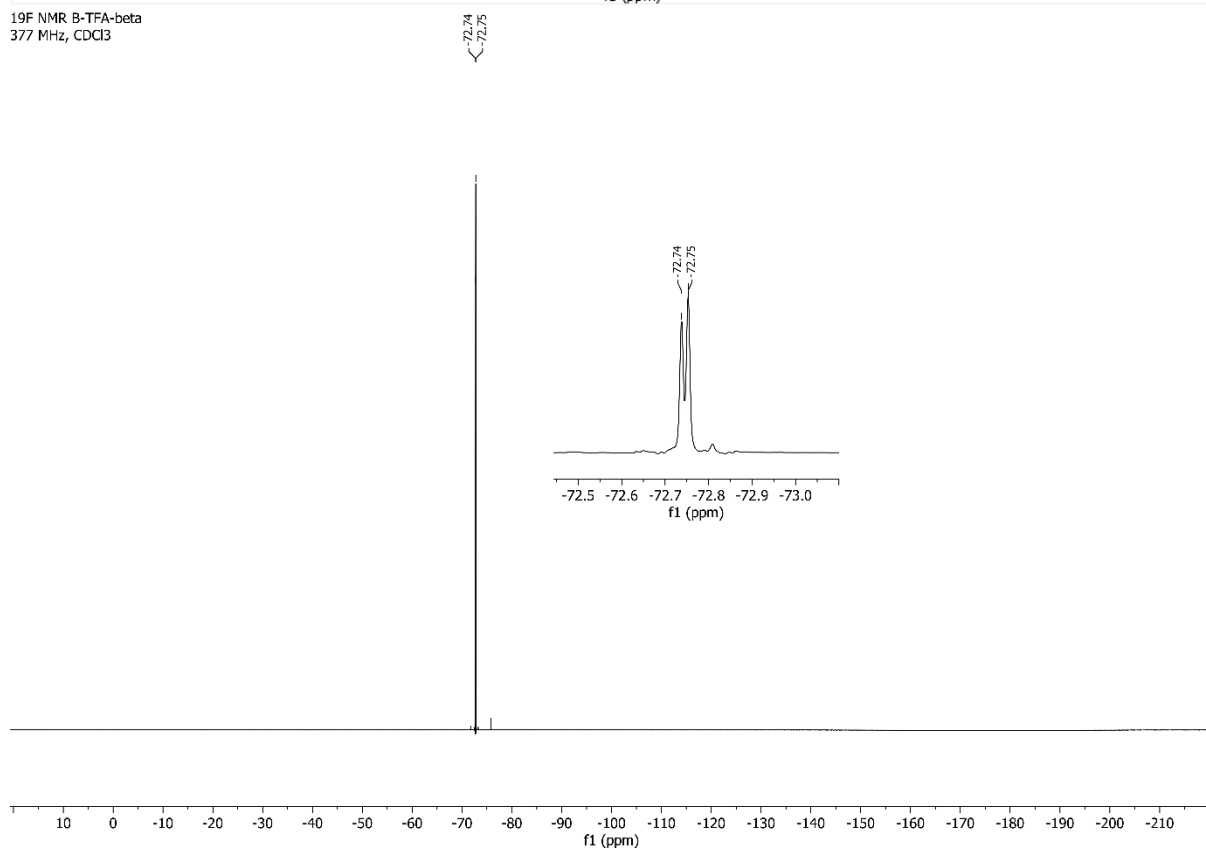
— 7.26 CDCl₃



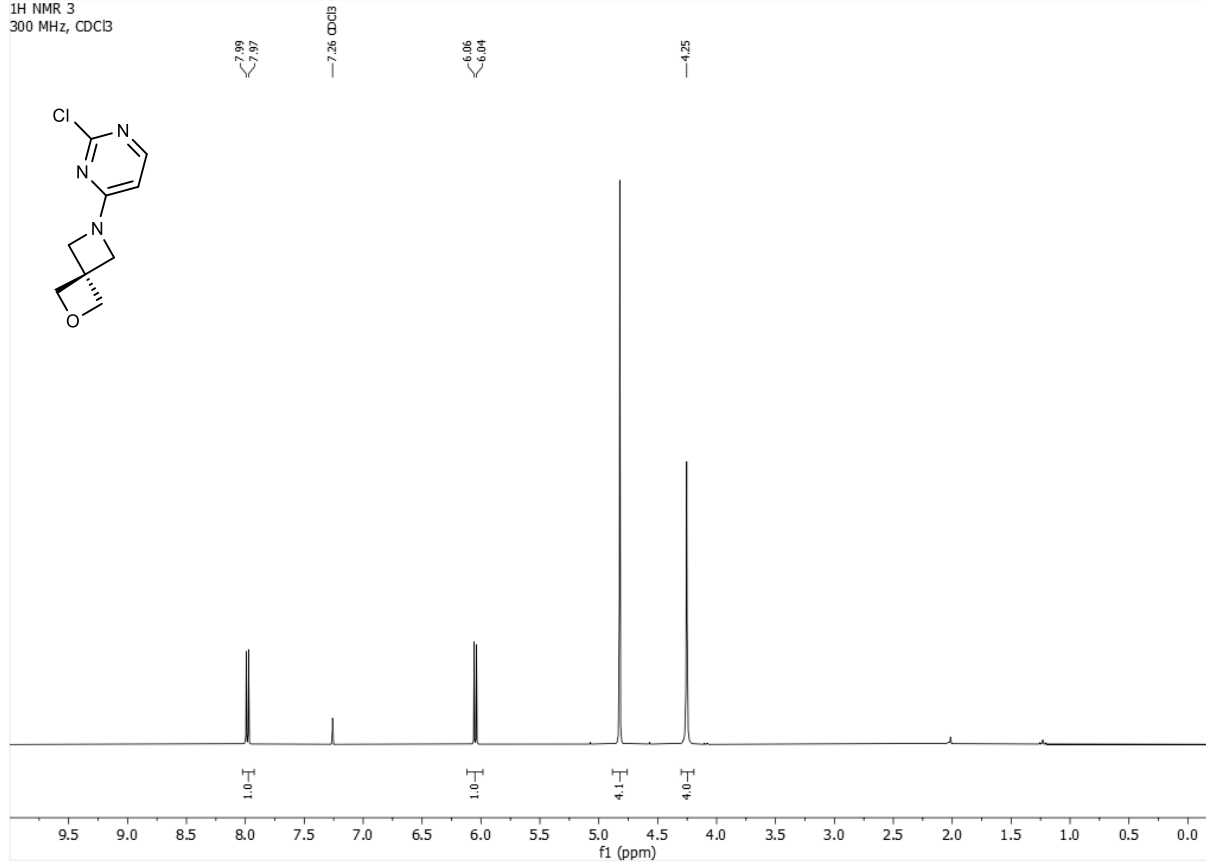
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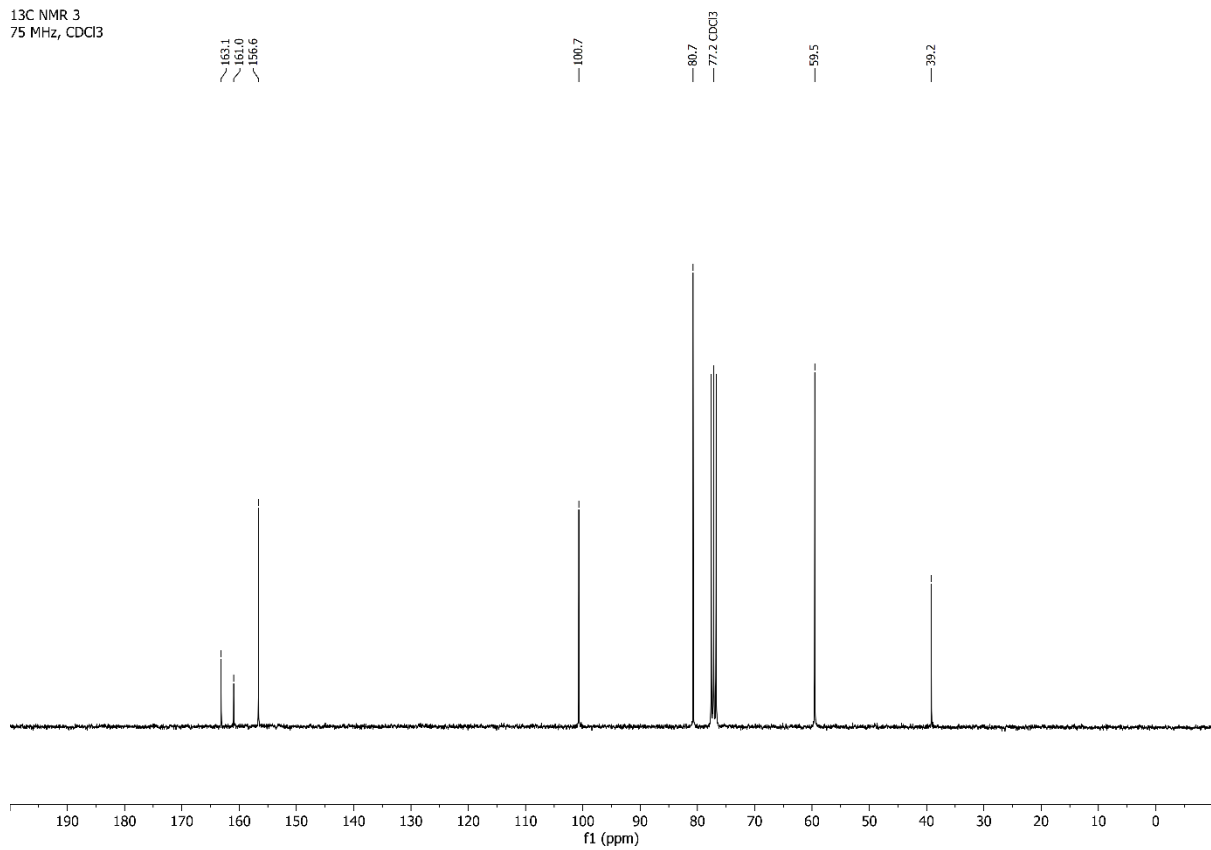
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377 MHz, CDCl₃



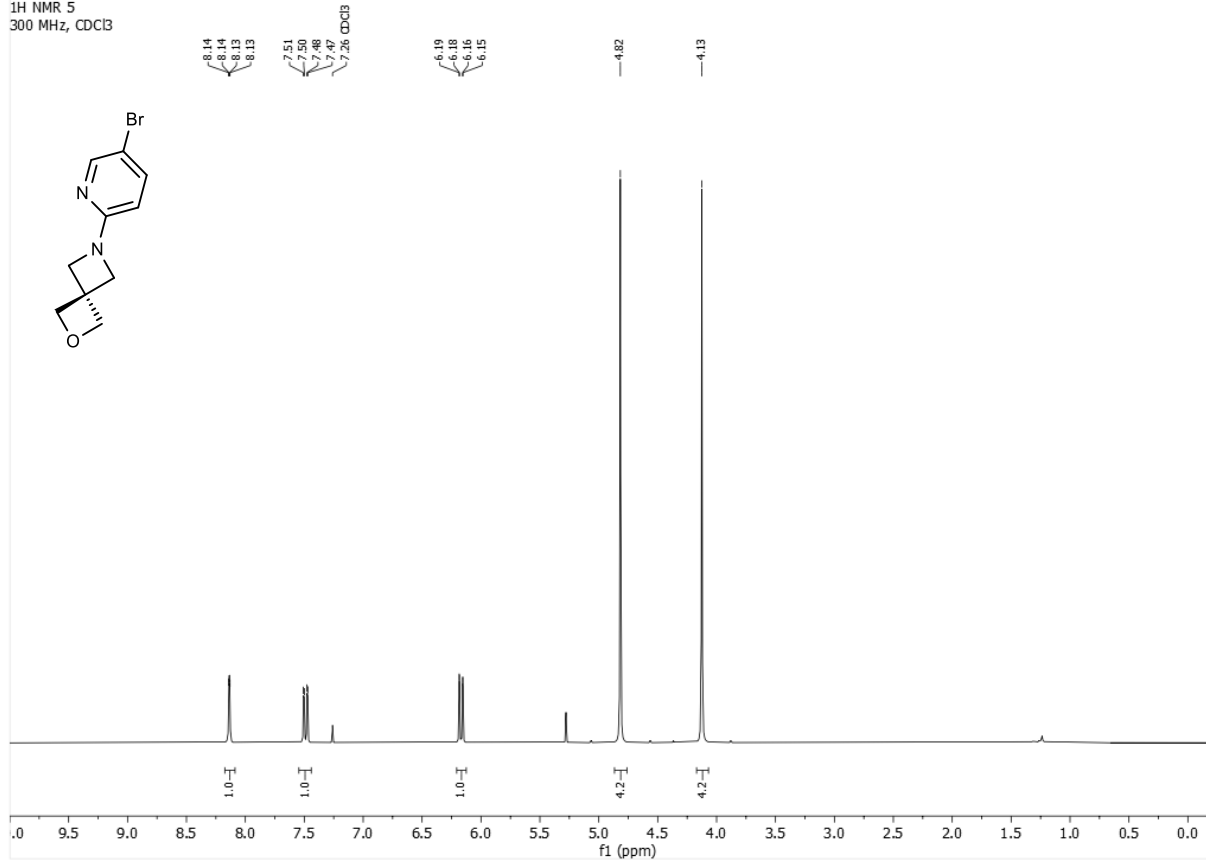
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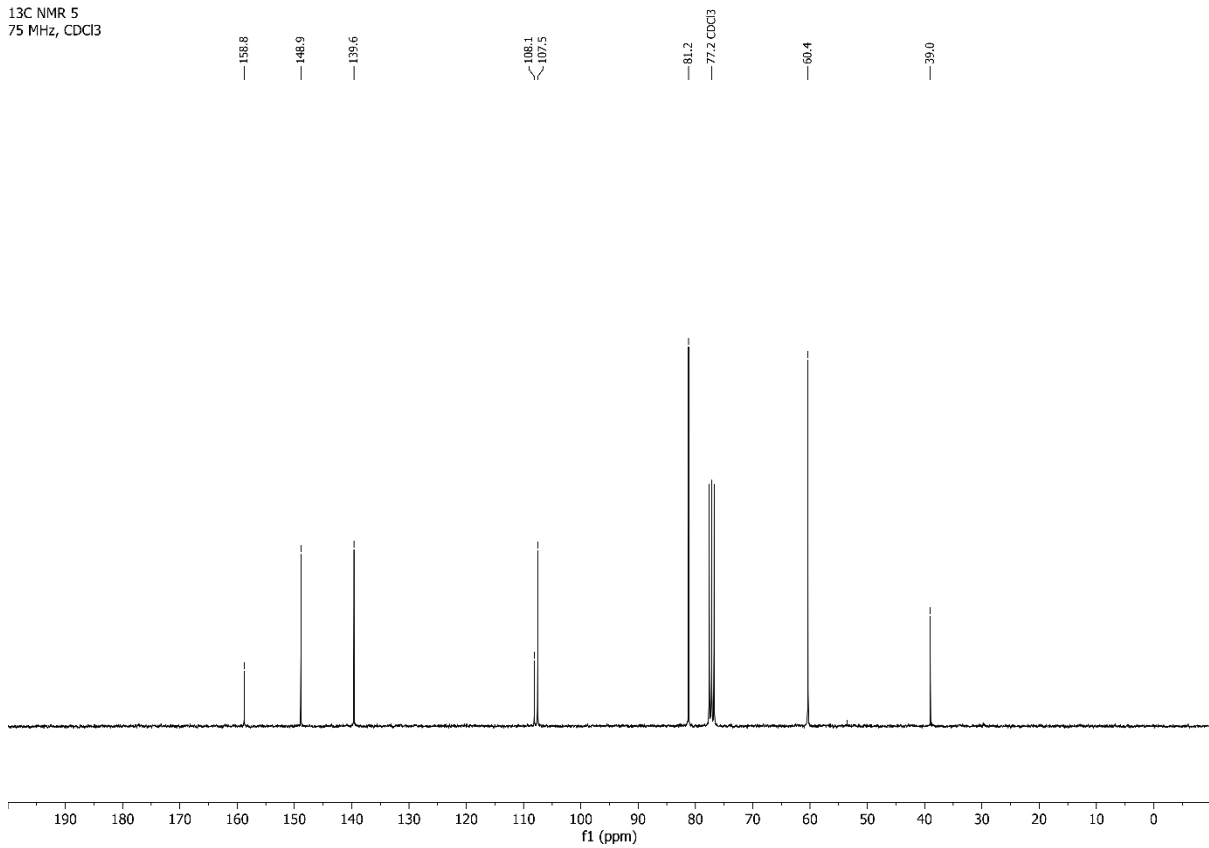
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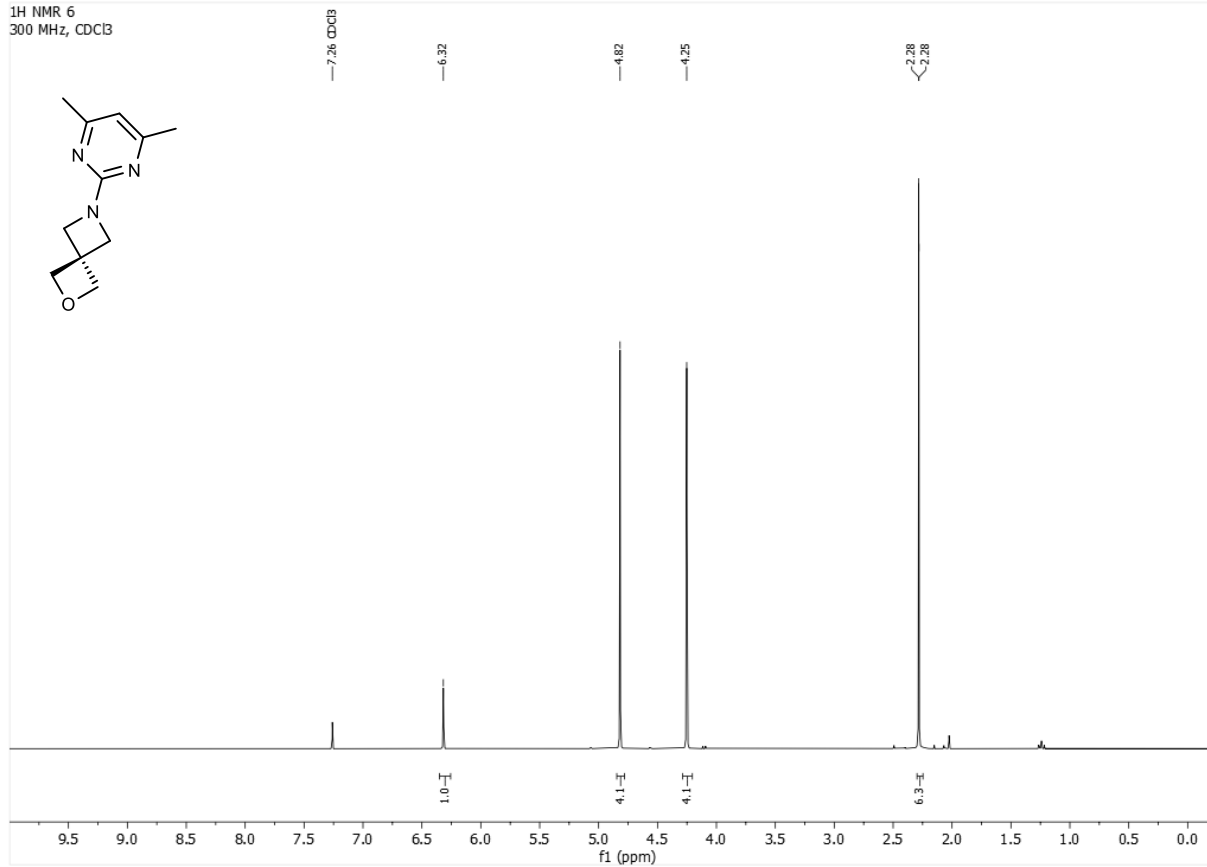
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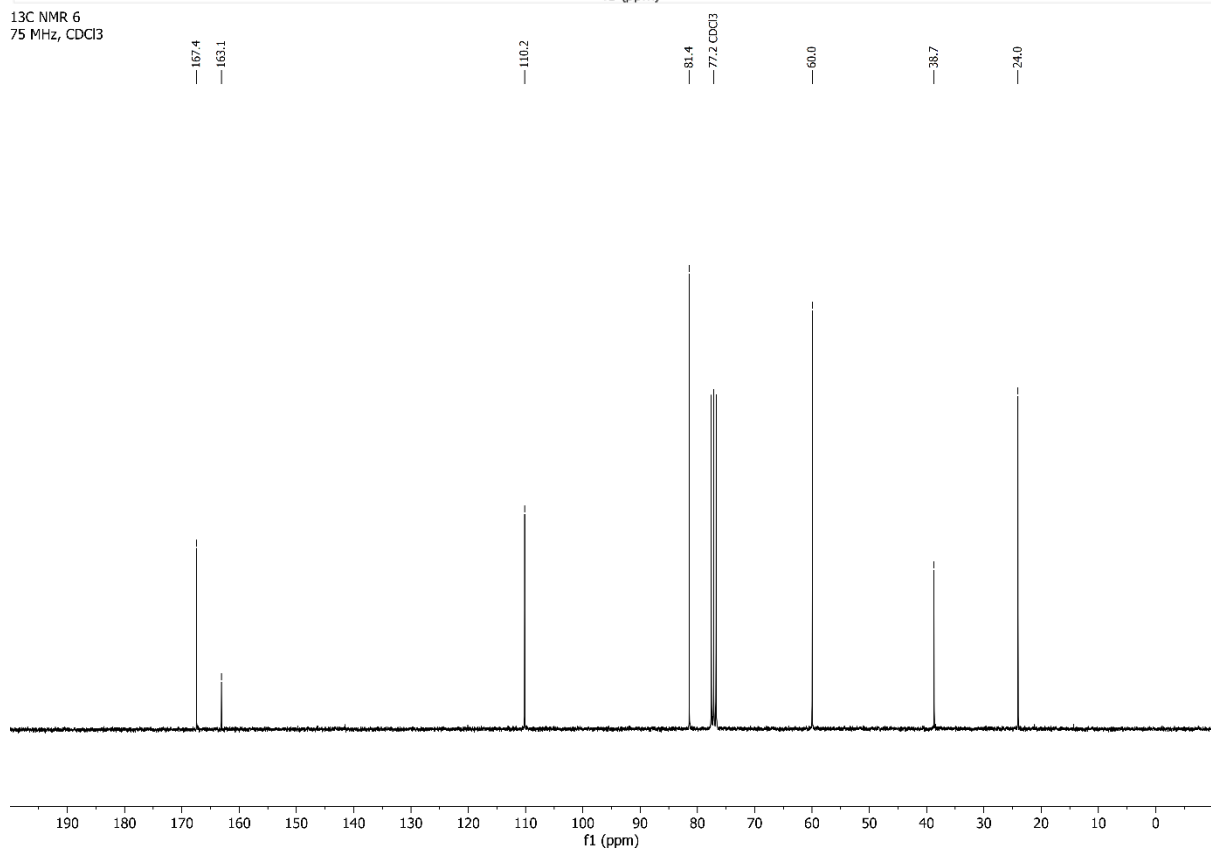
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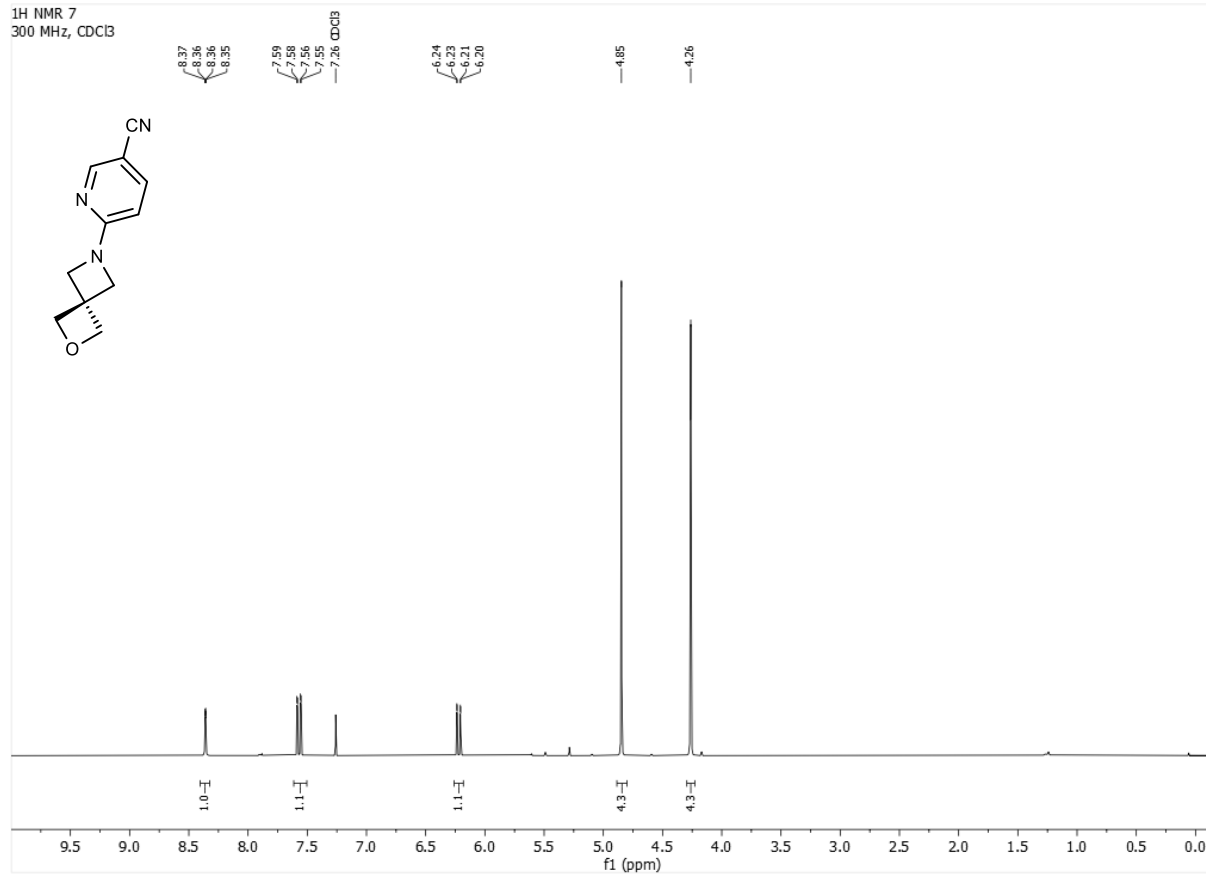
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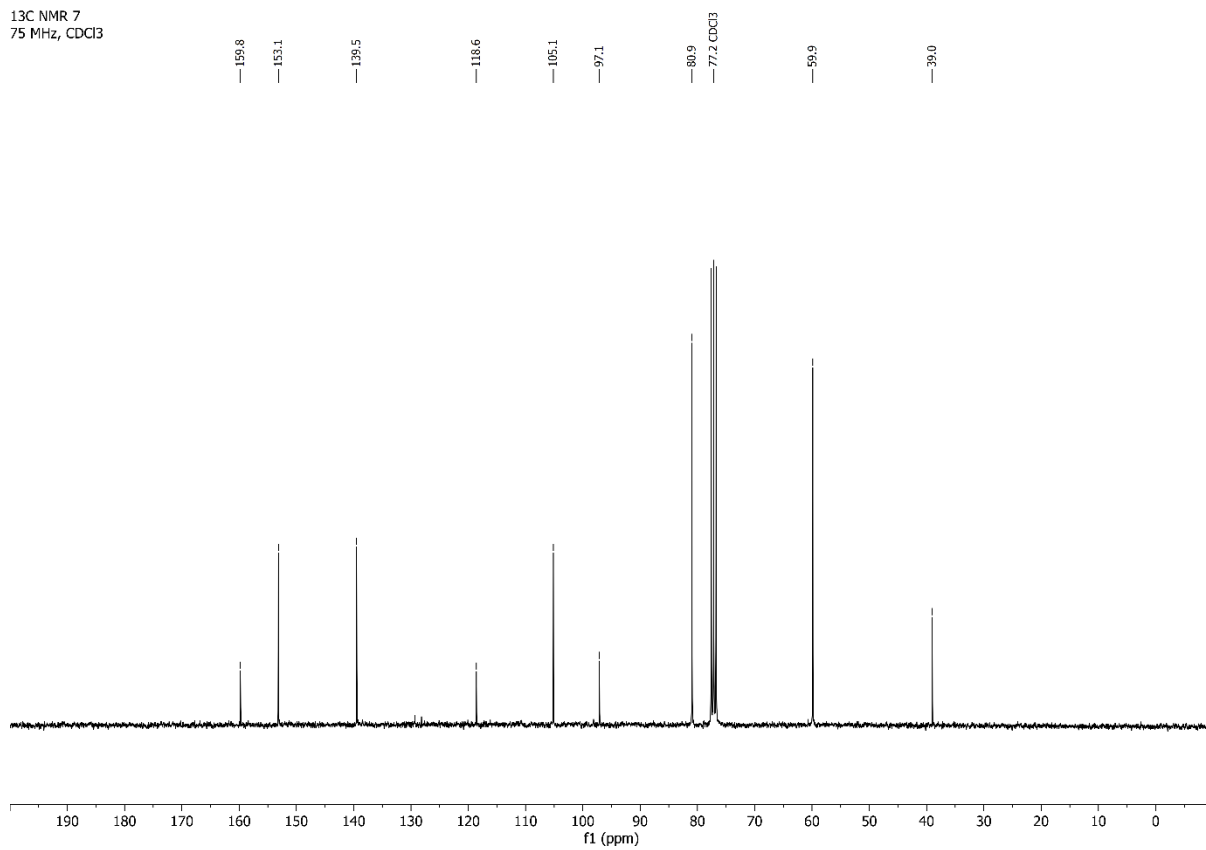
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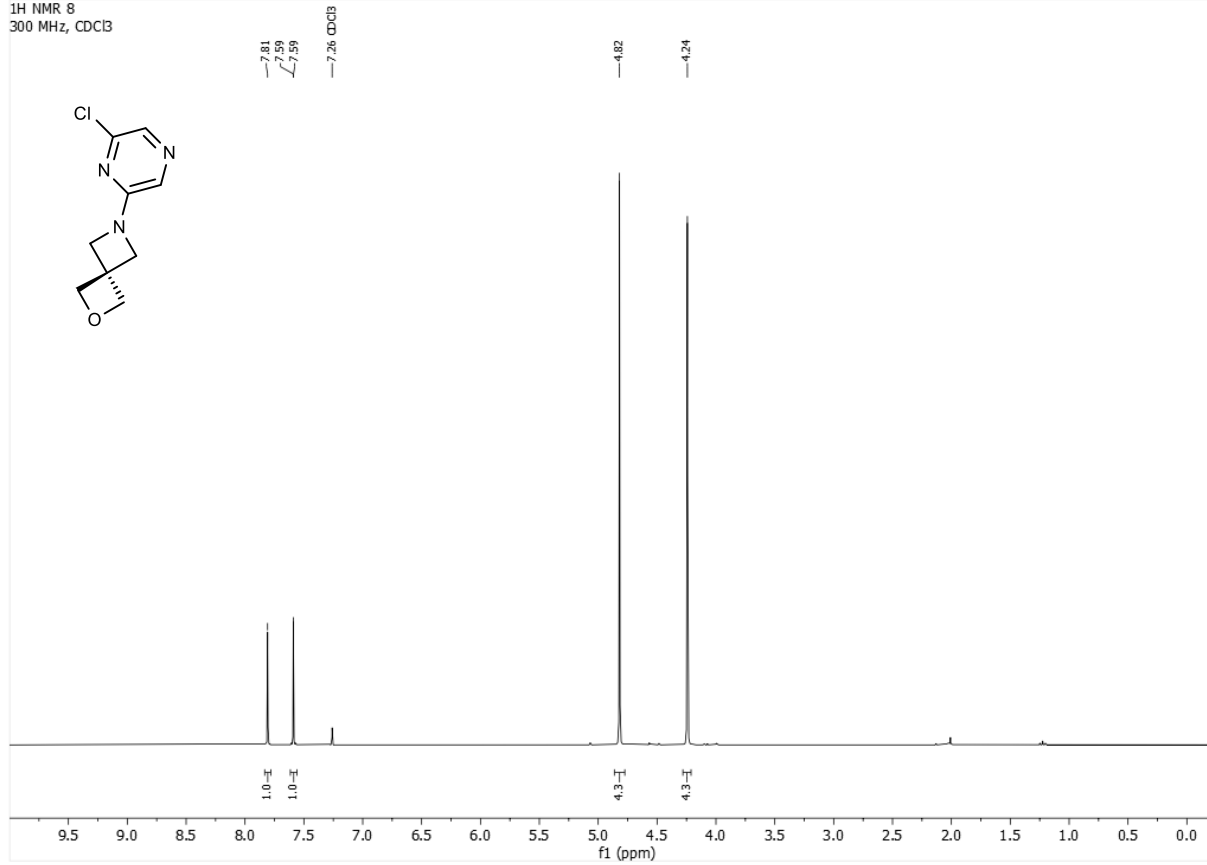
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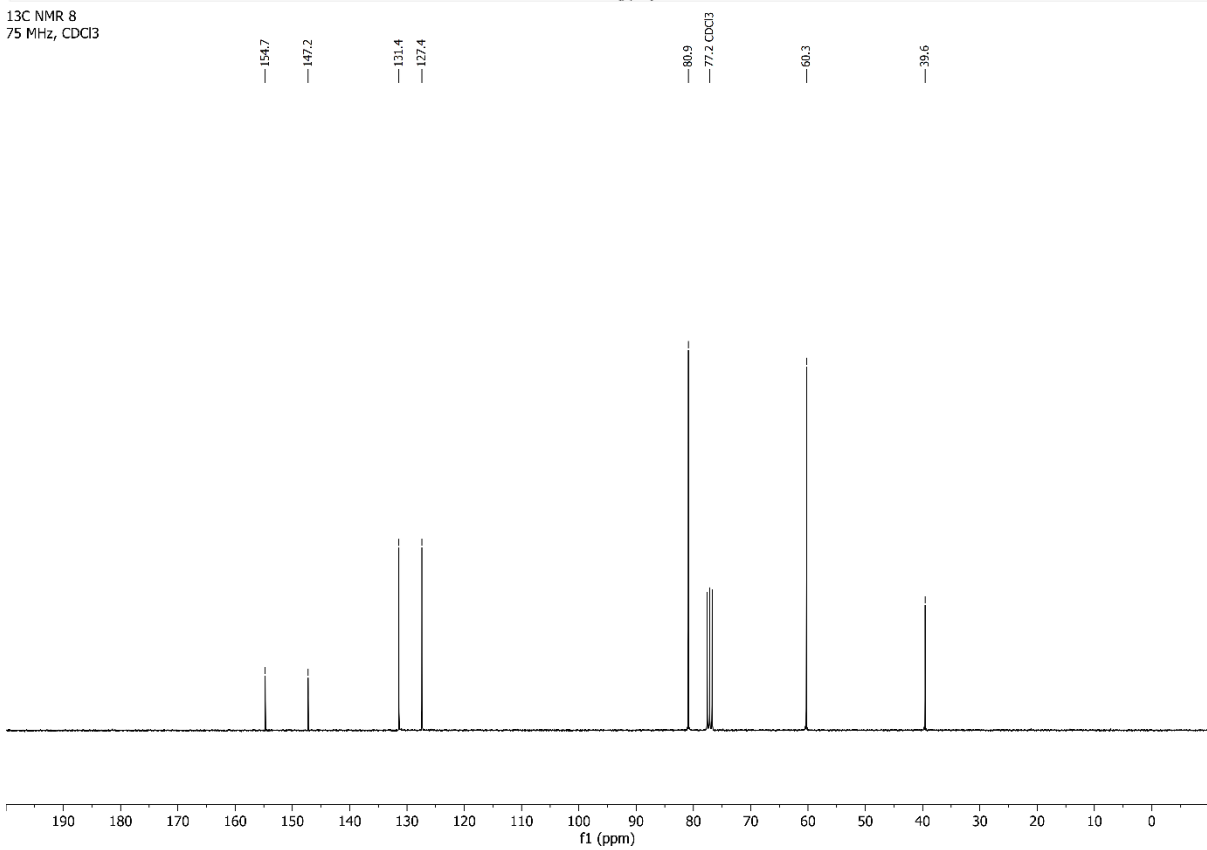
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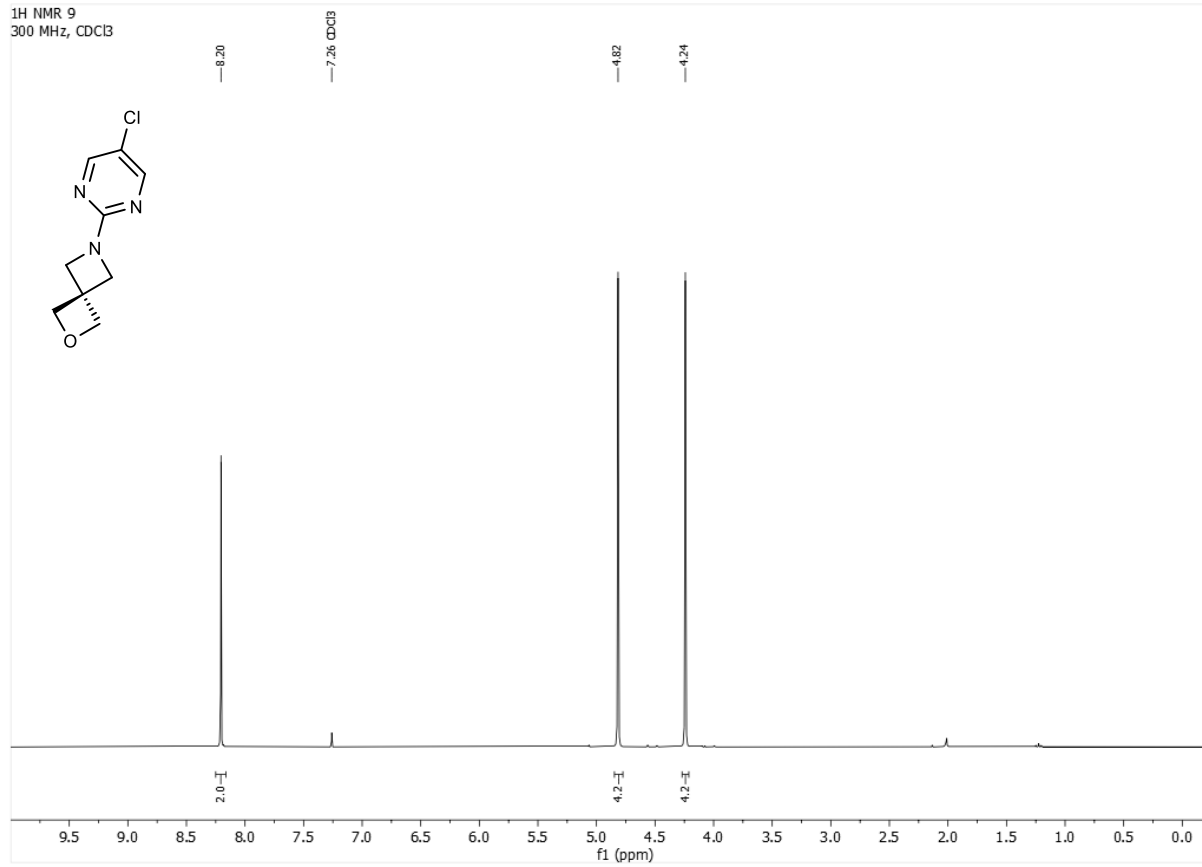
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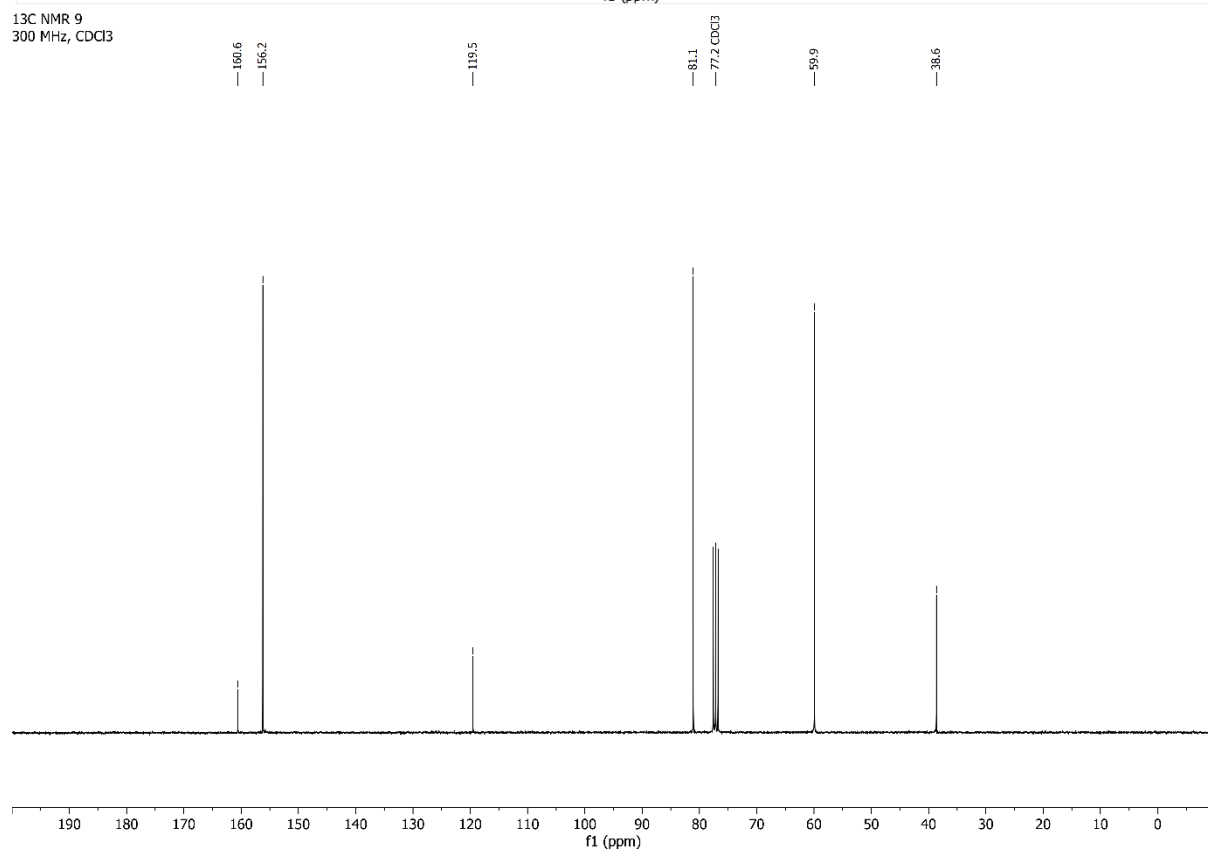
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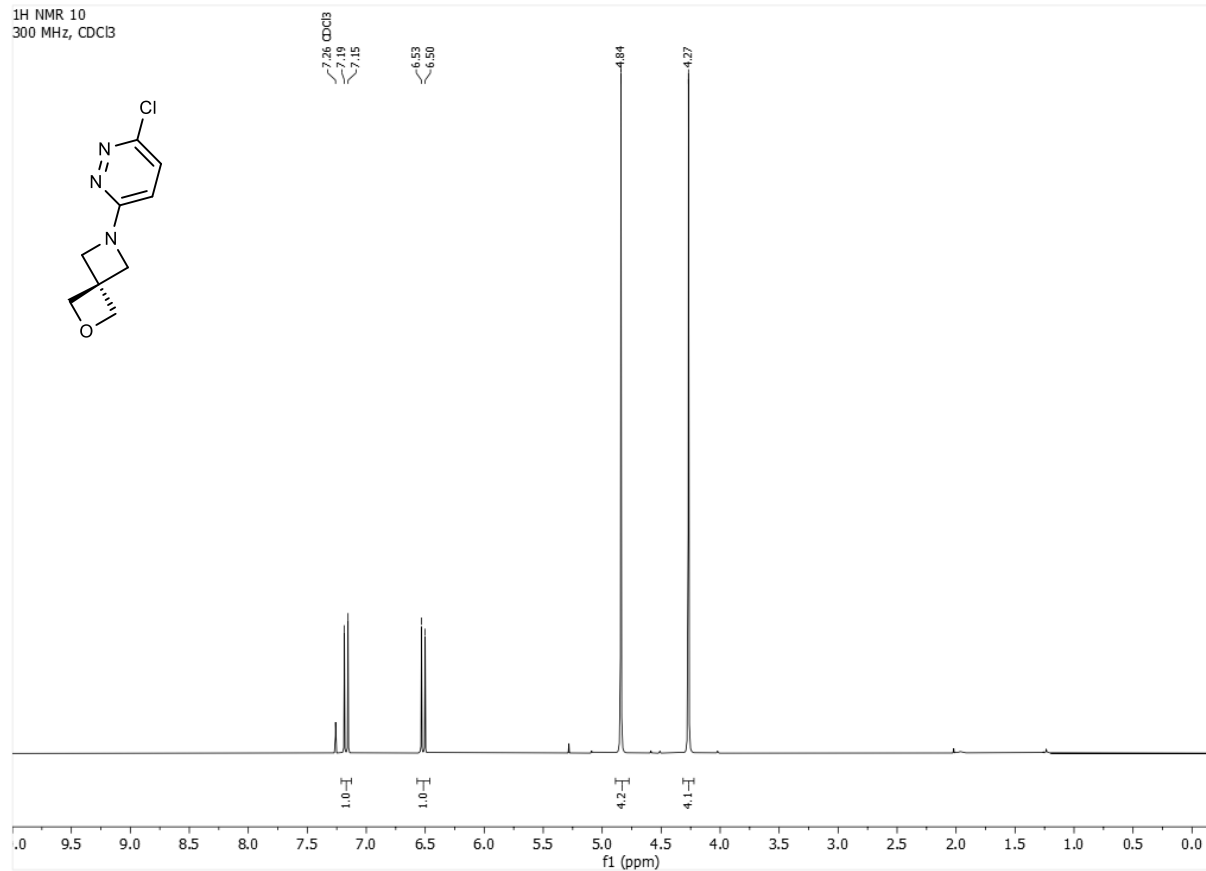
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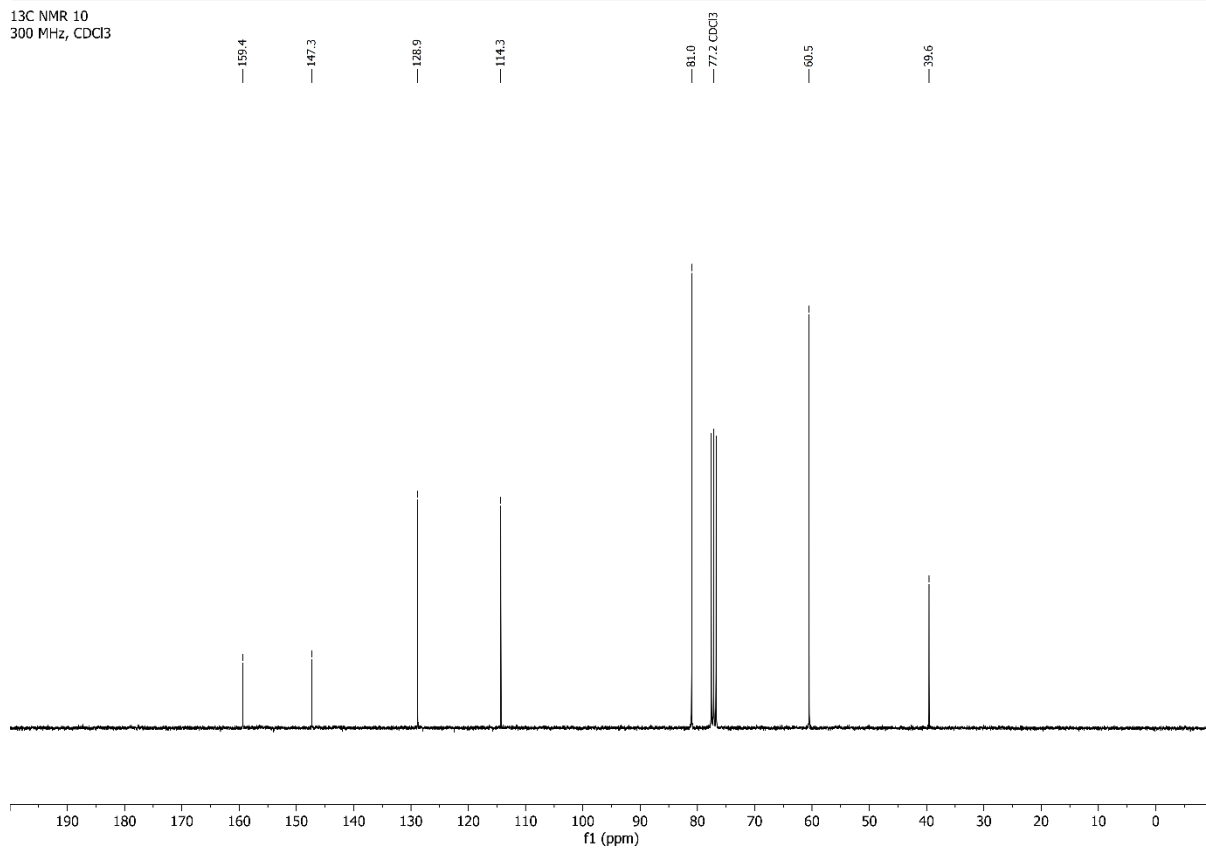
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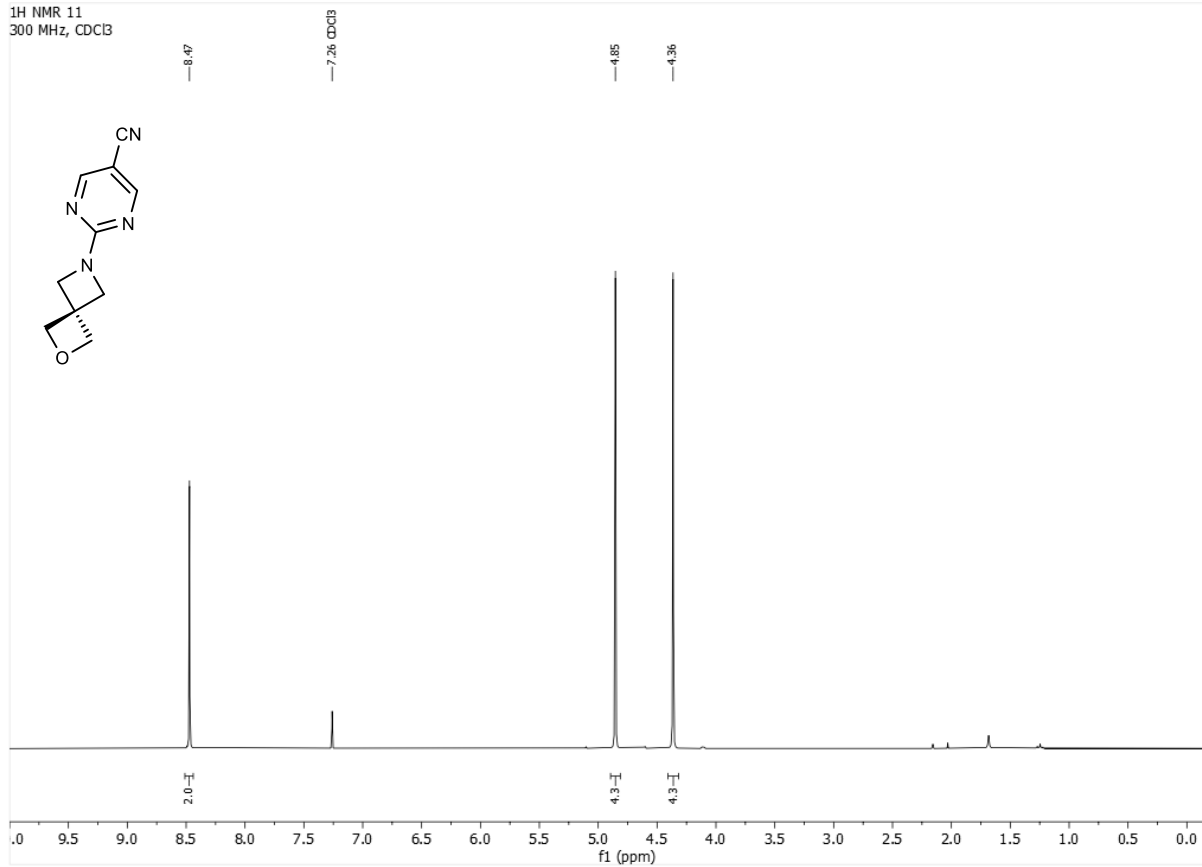
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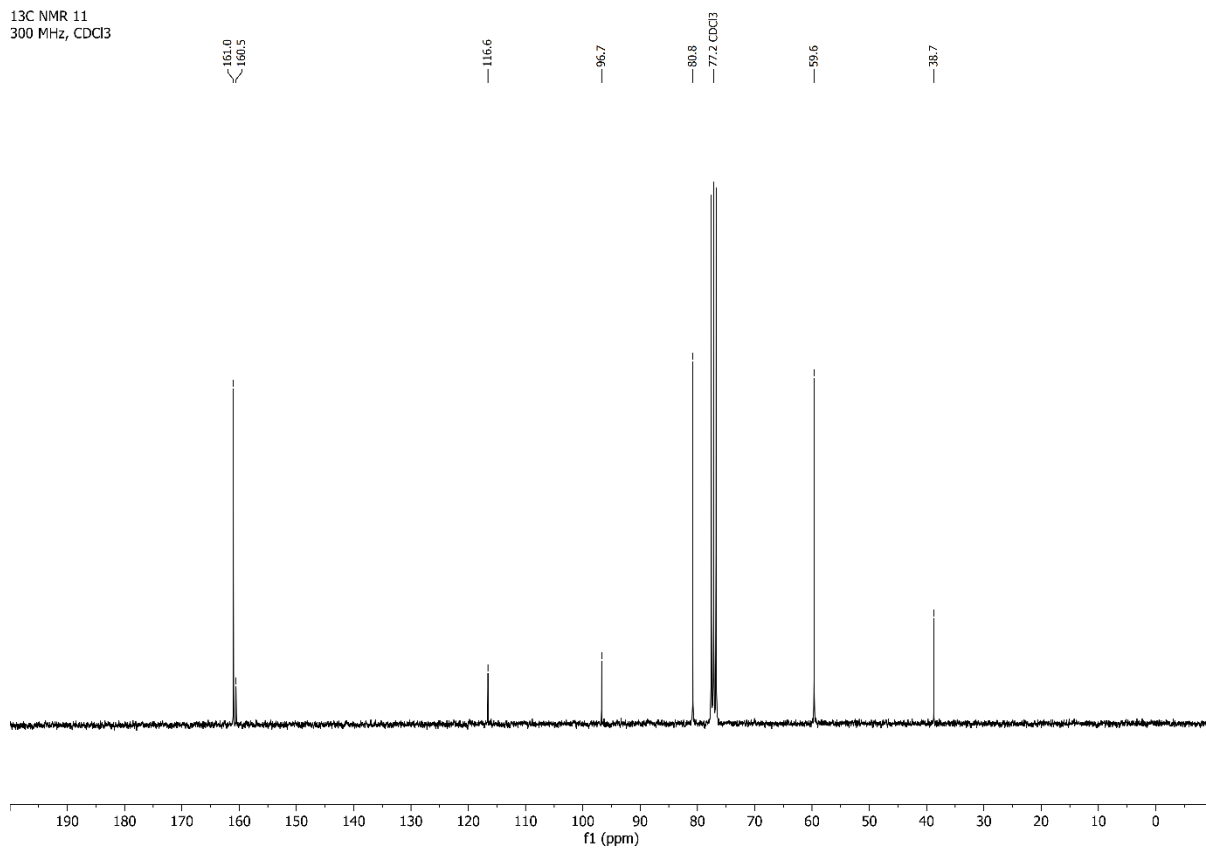
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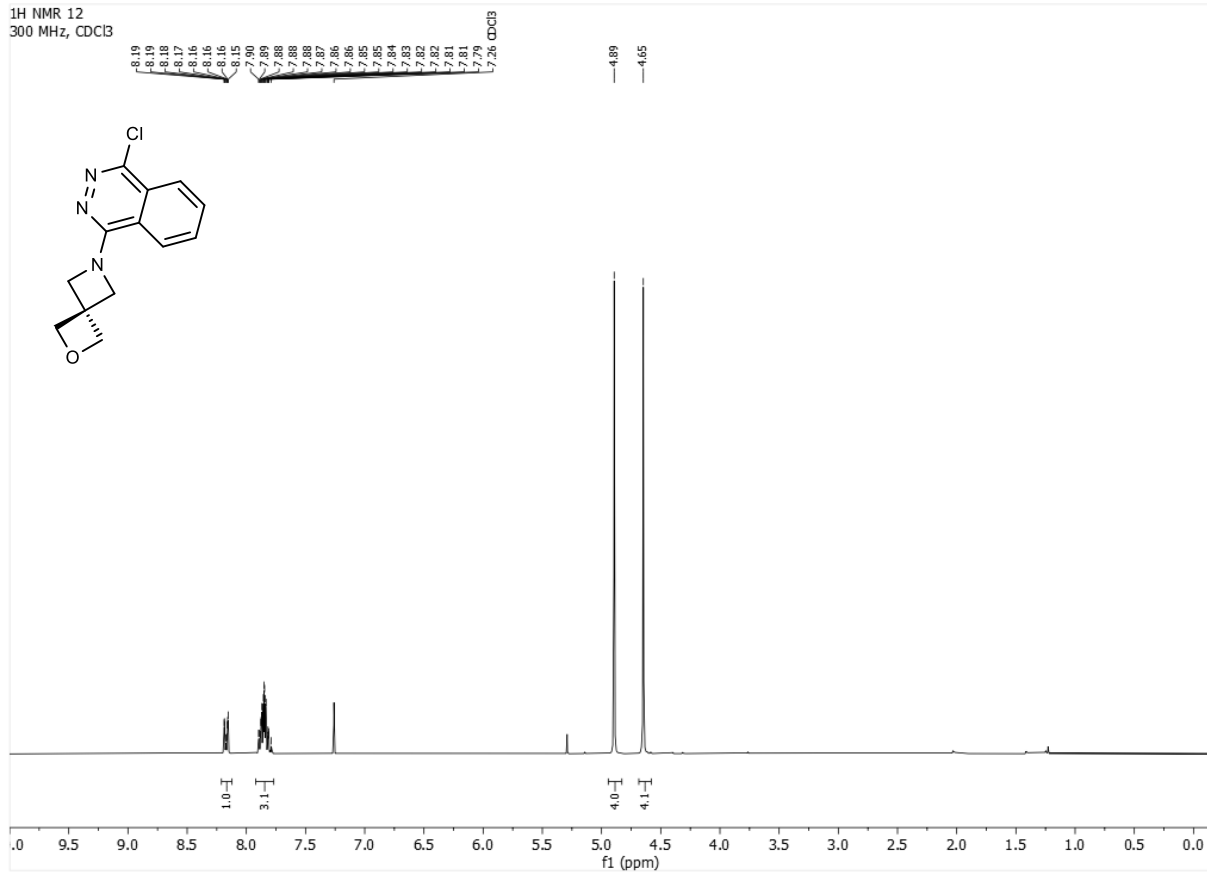
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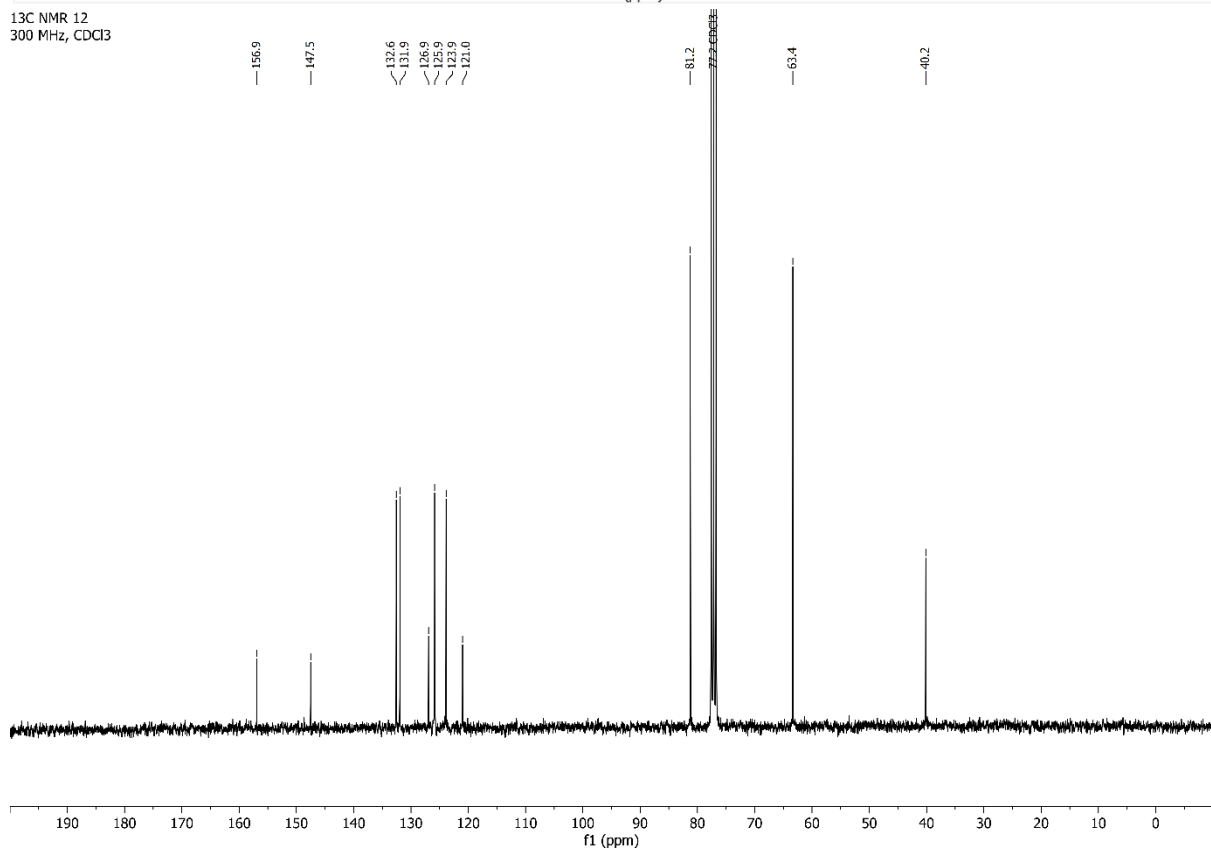
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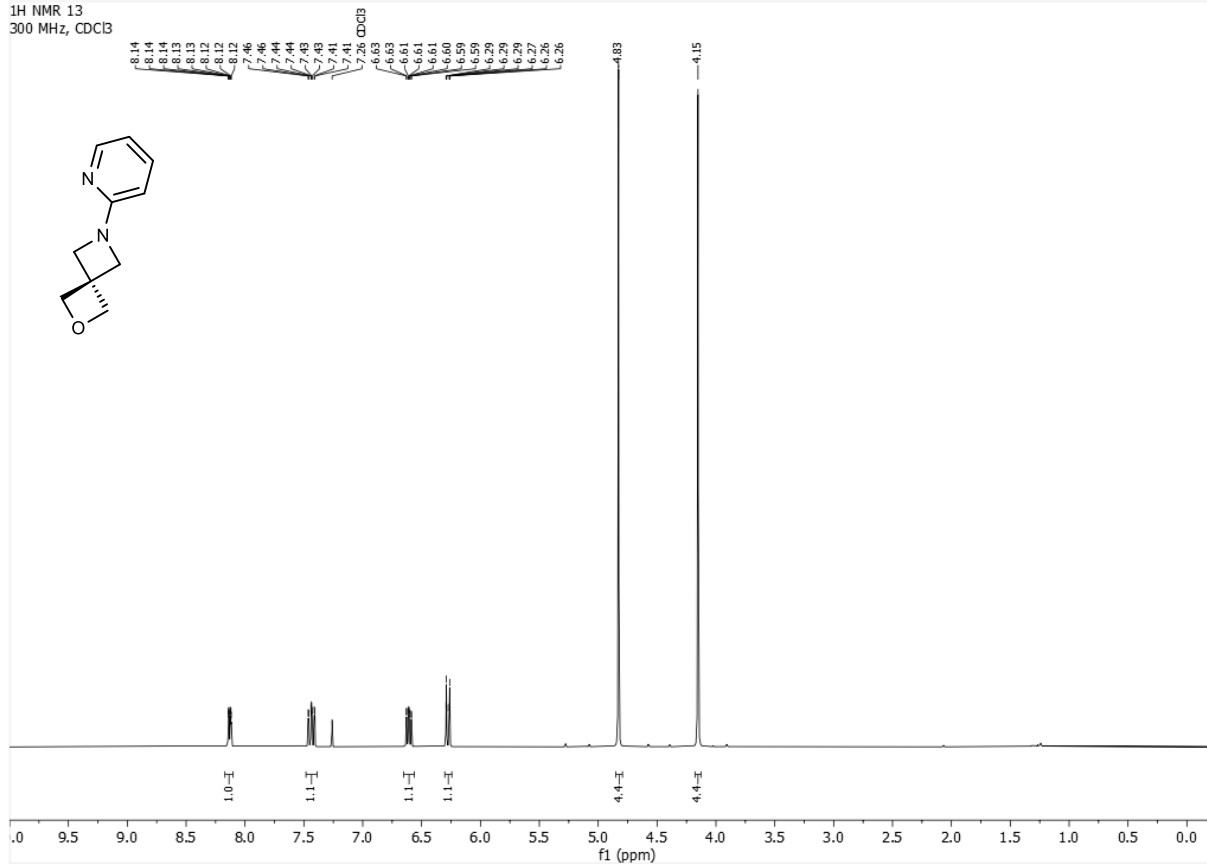
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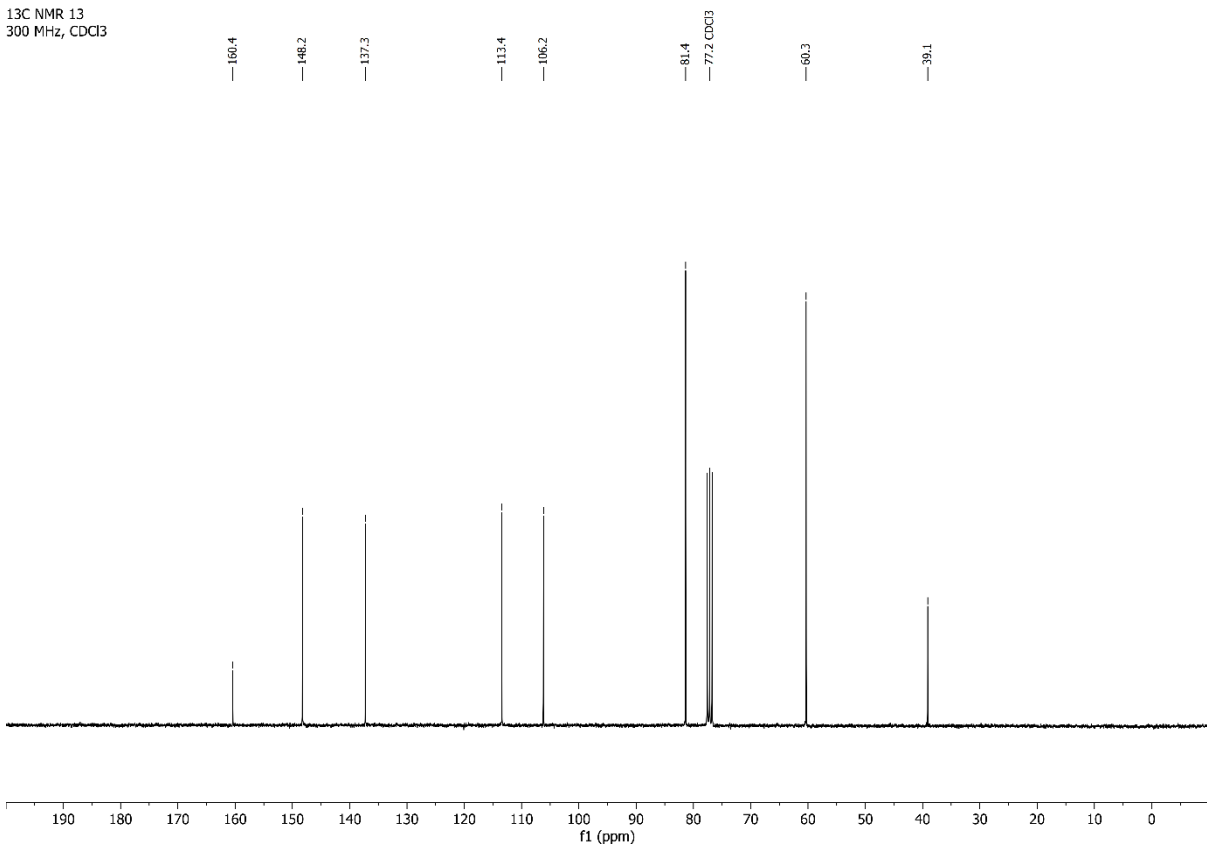
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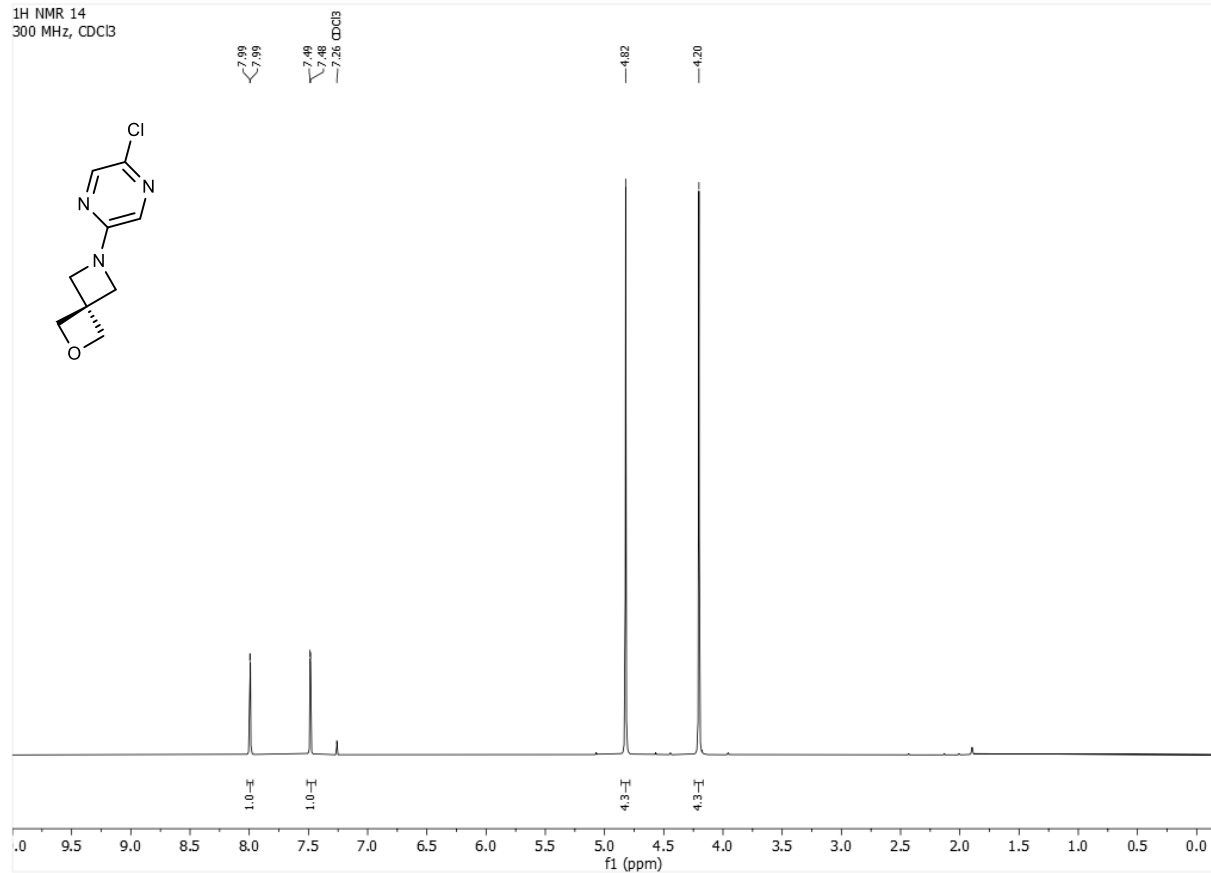
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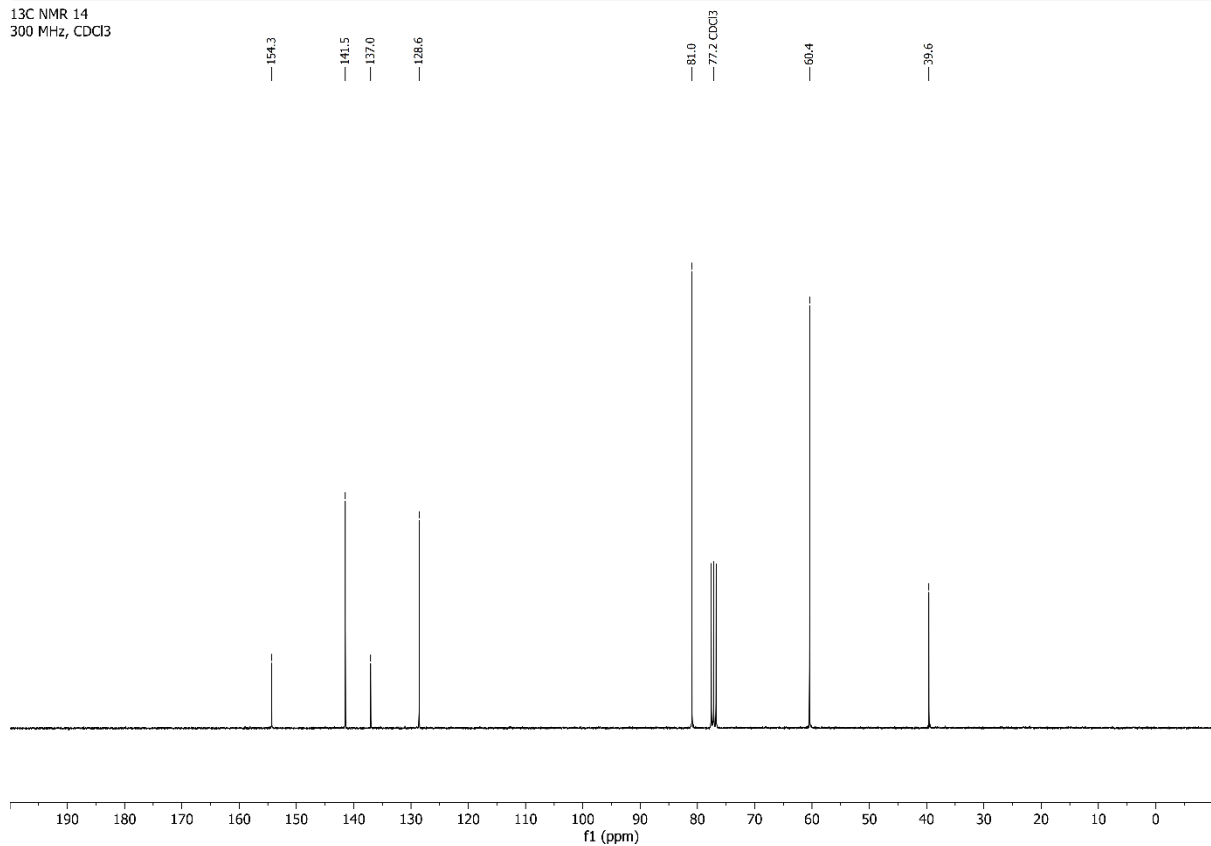
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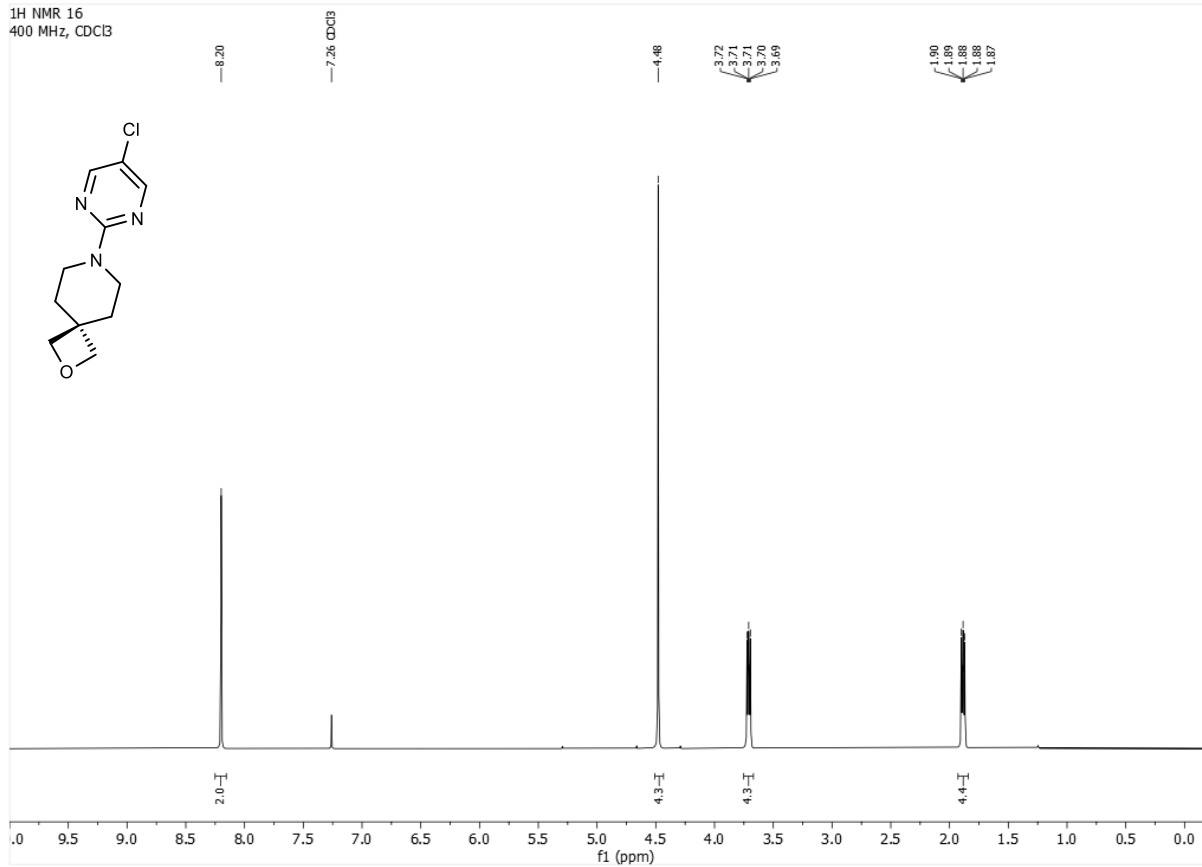
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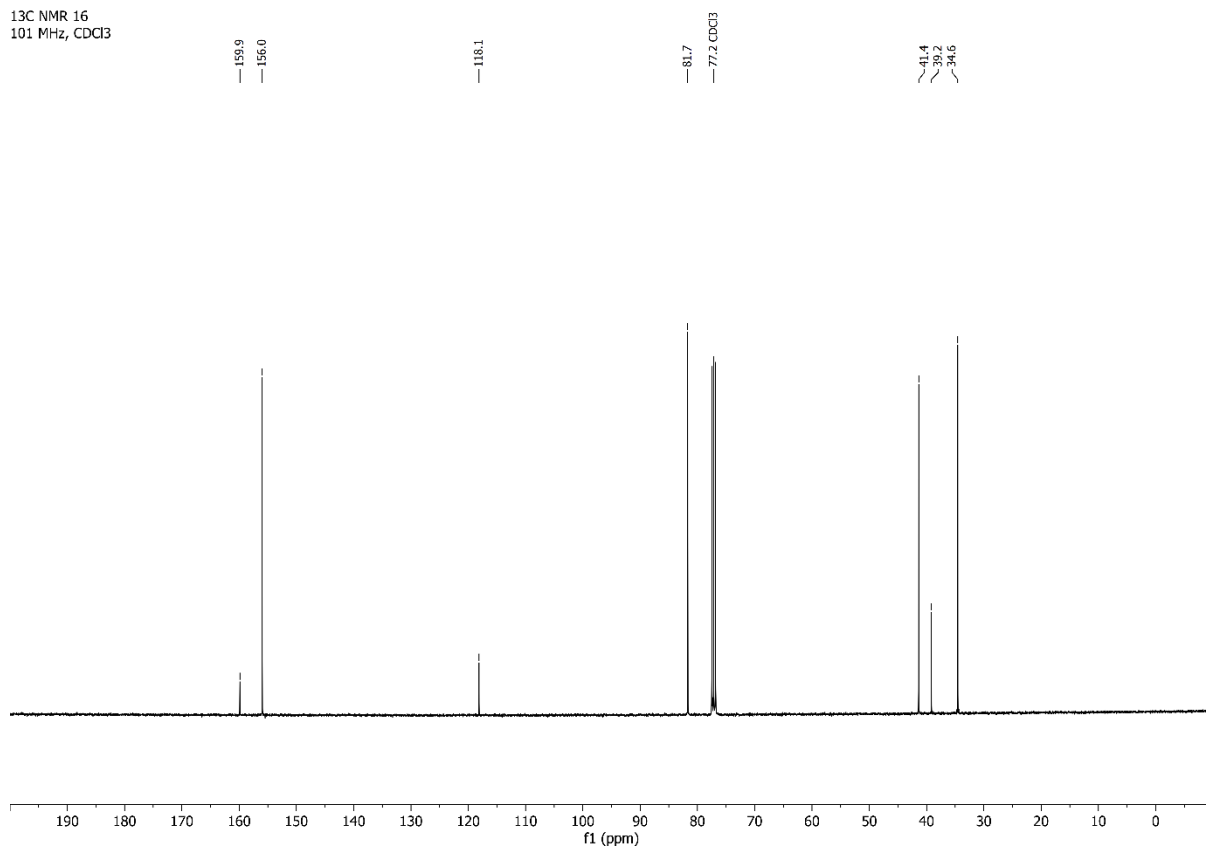
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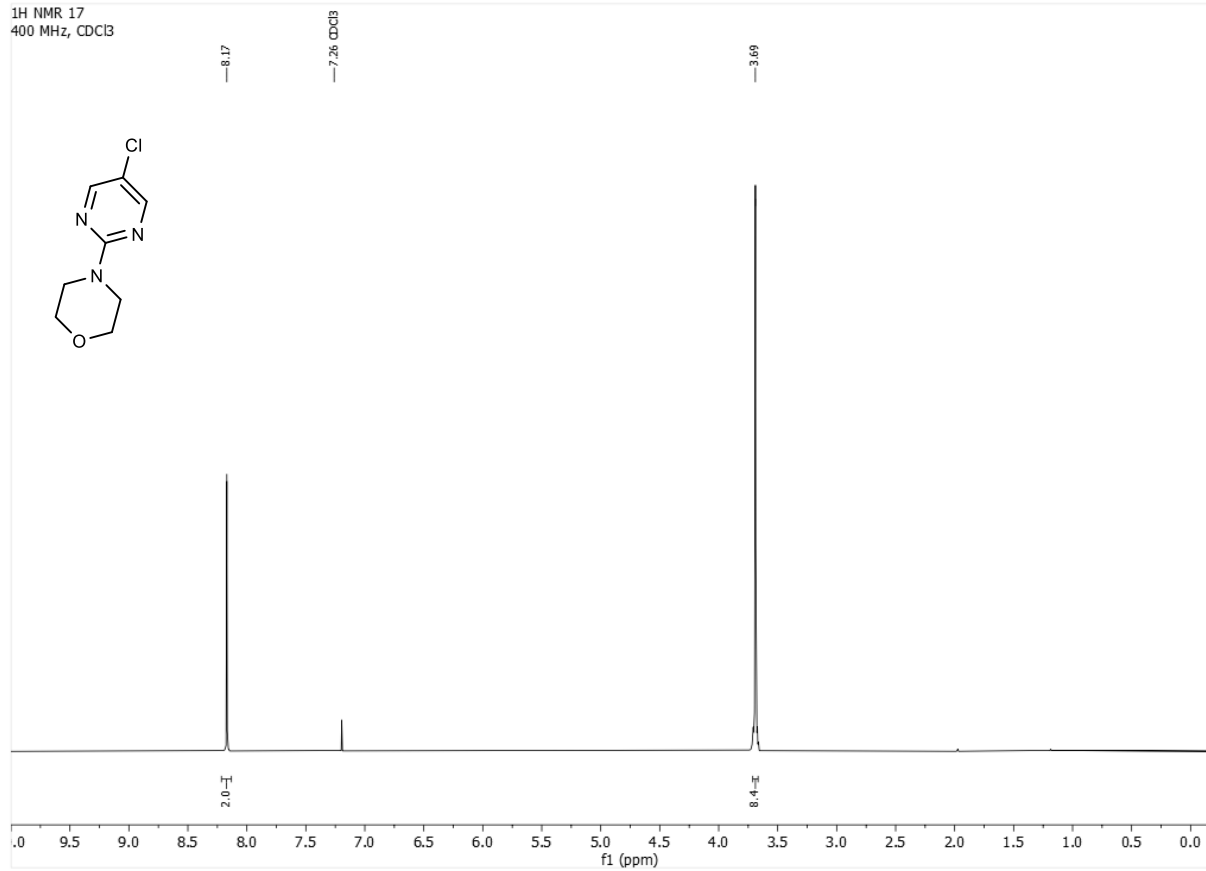
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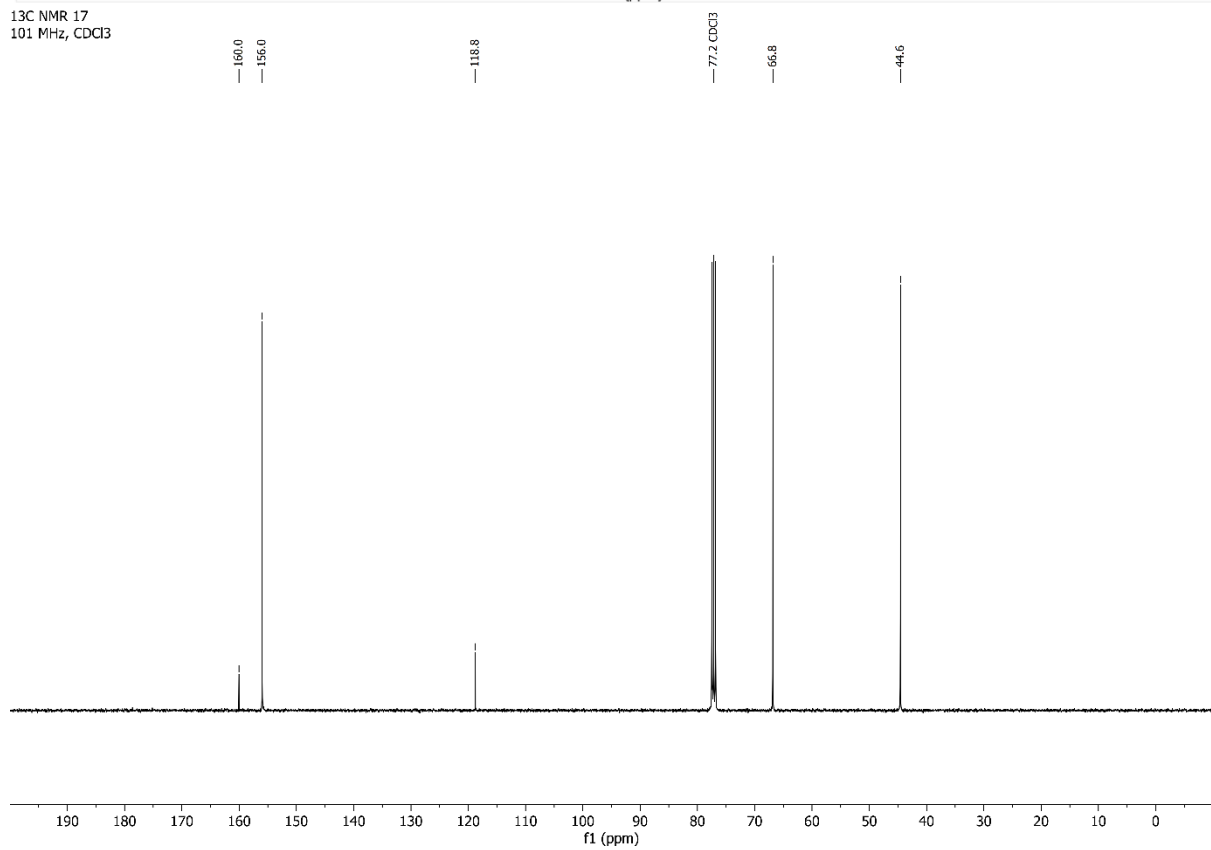
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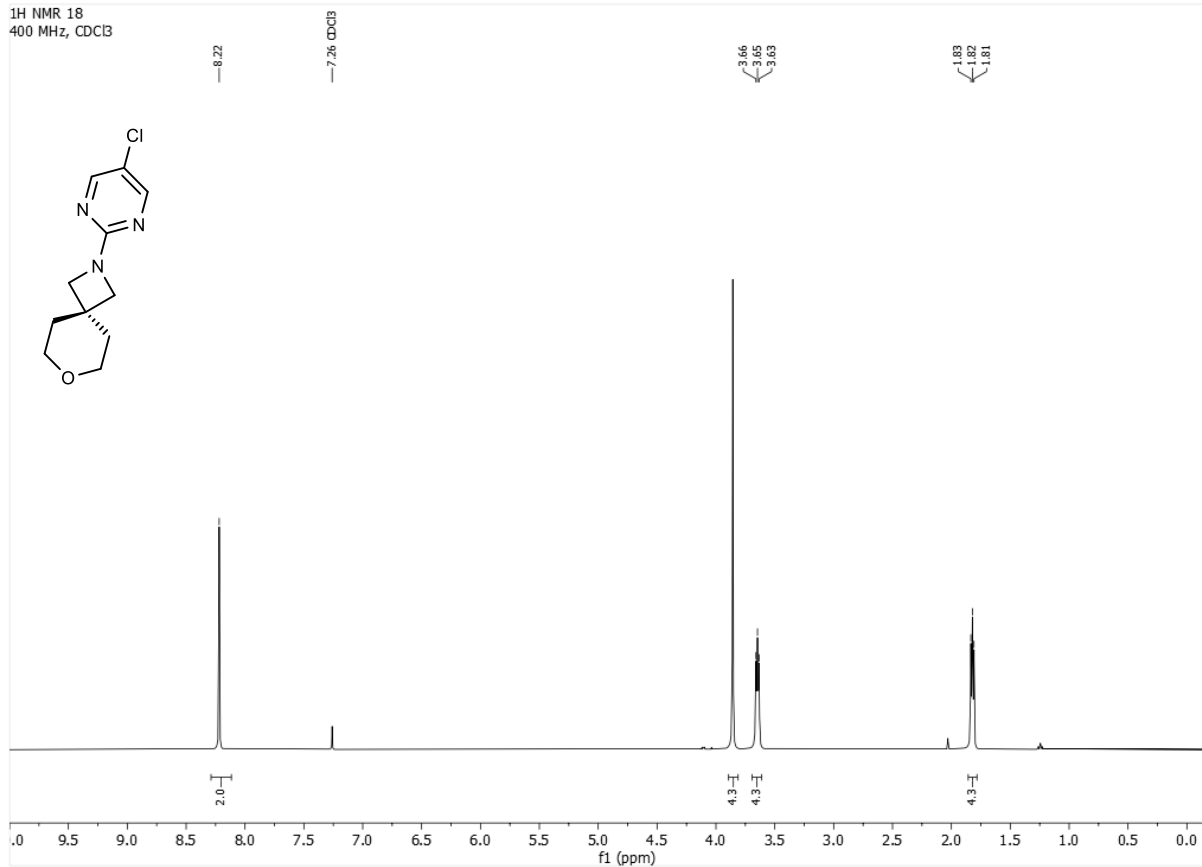
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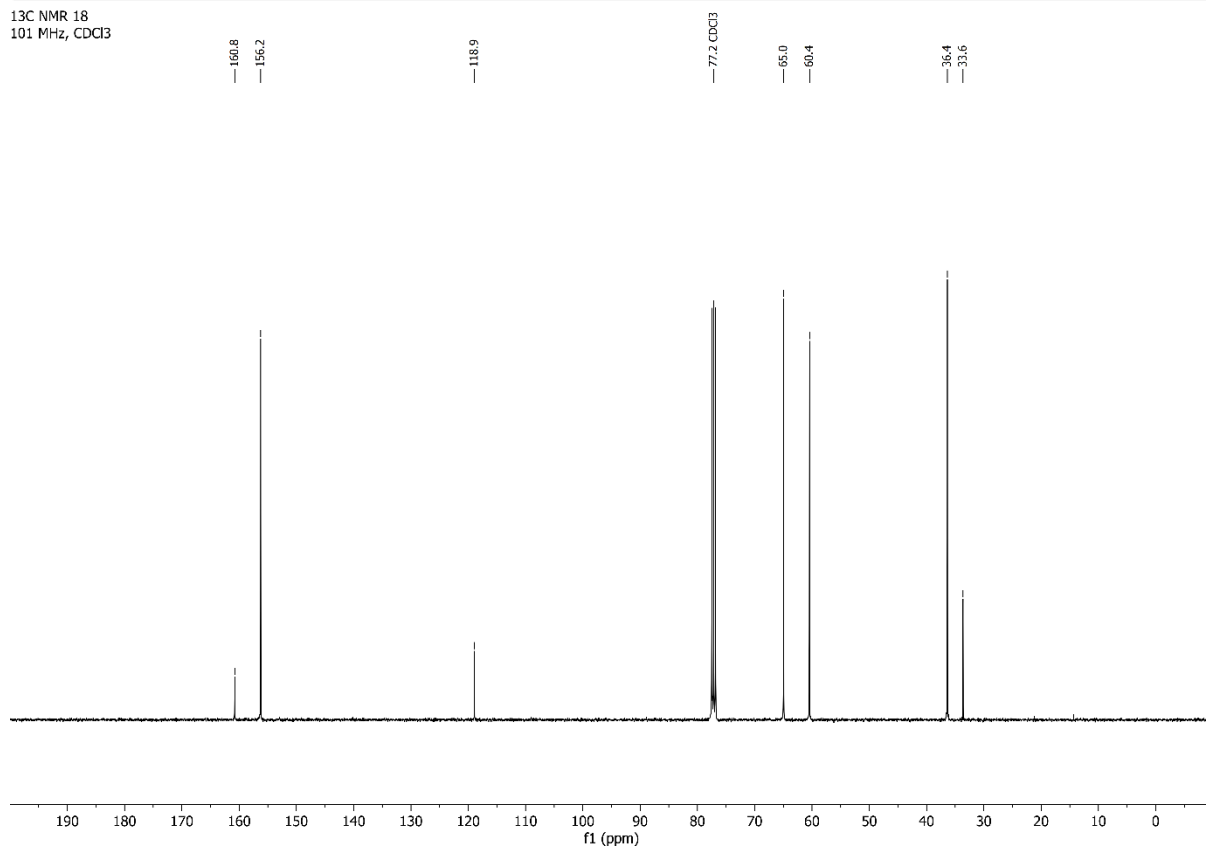
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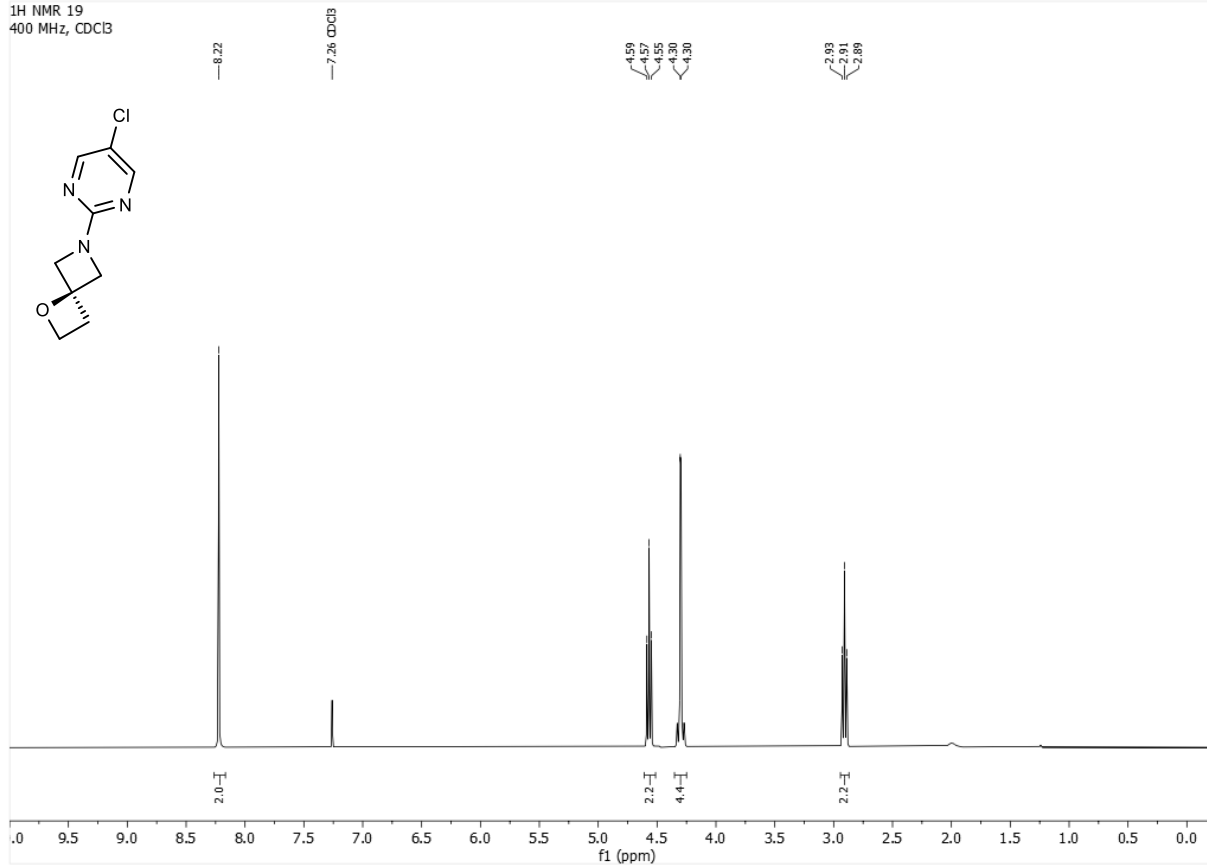
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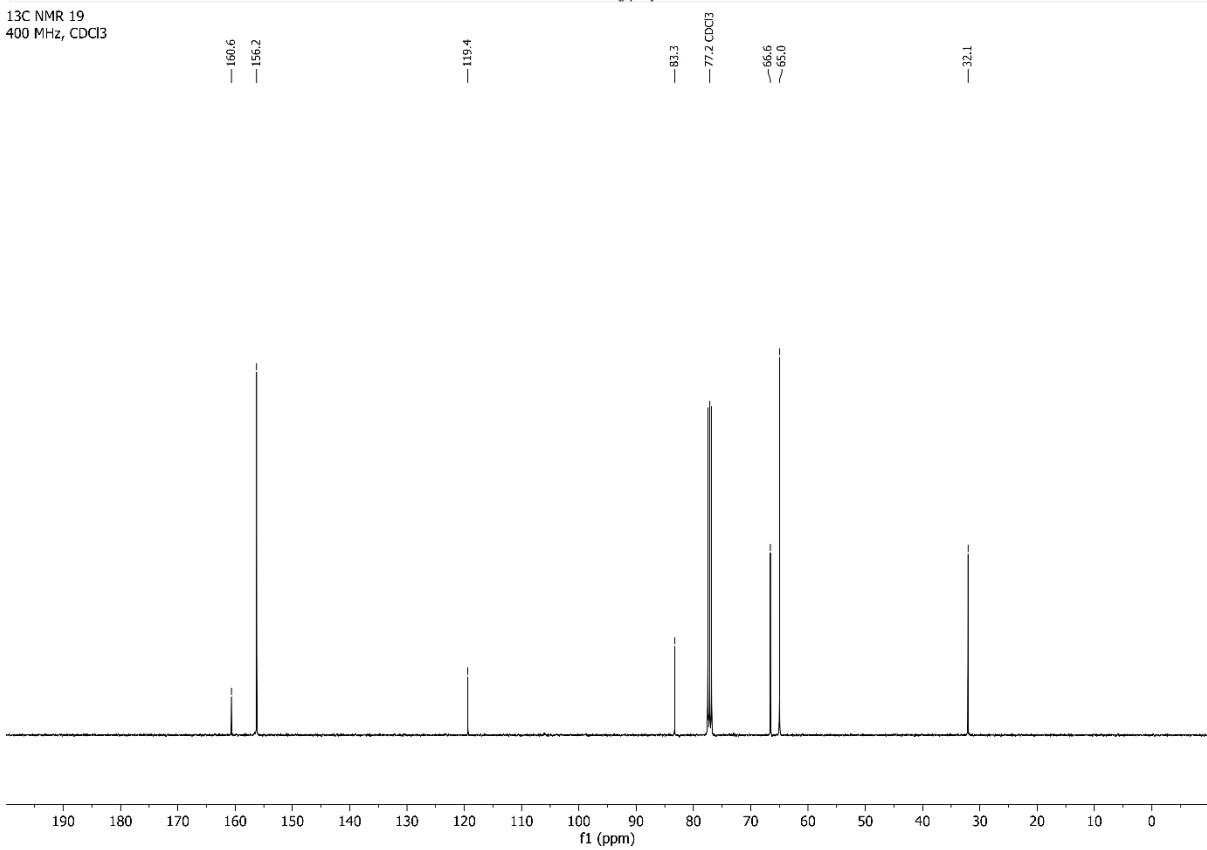
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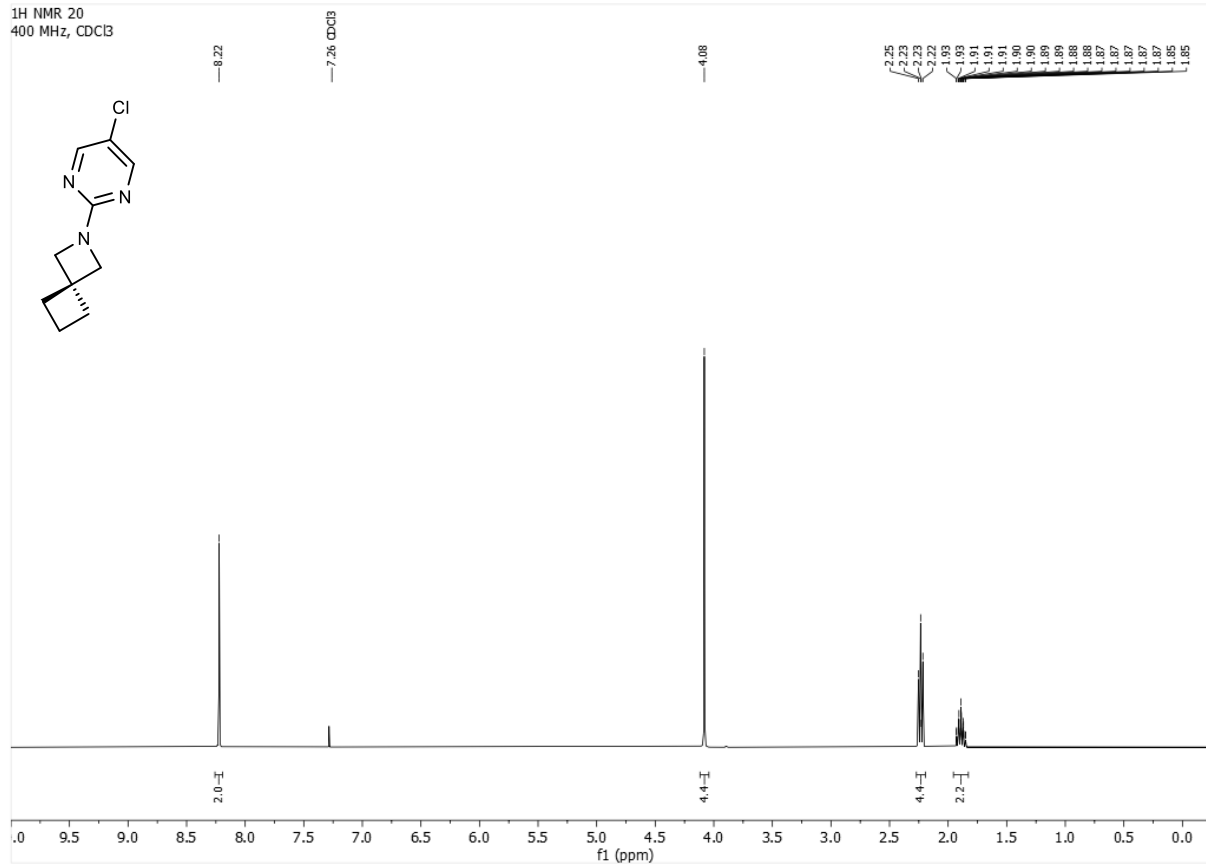
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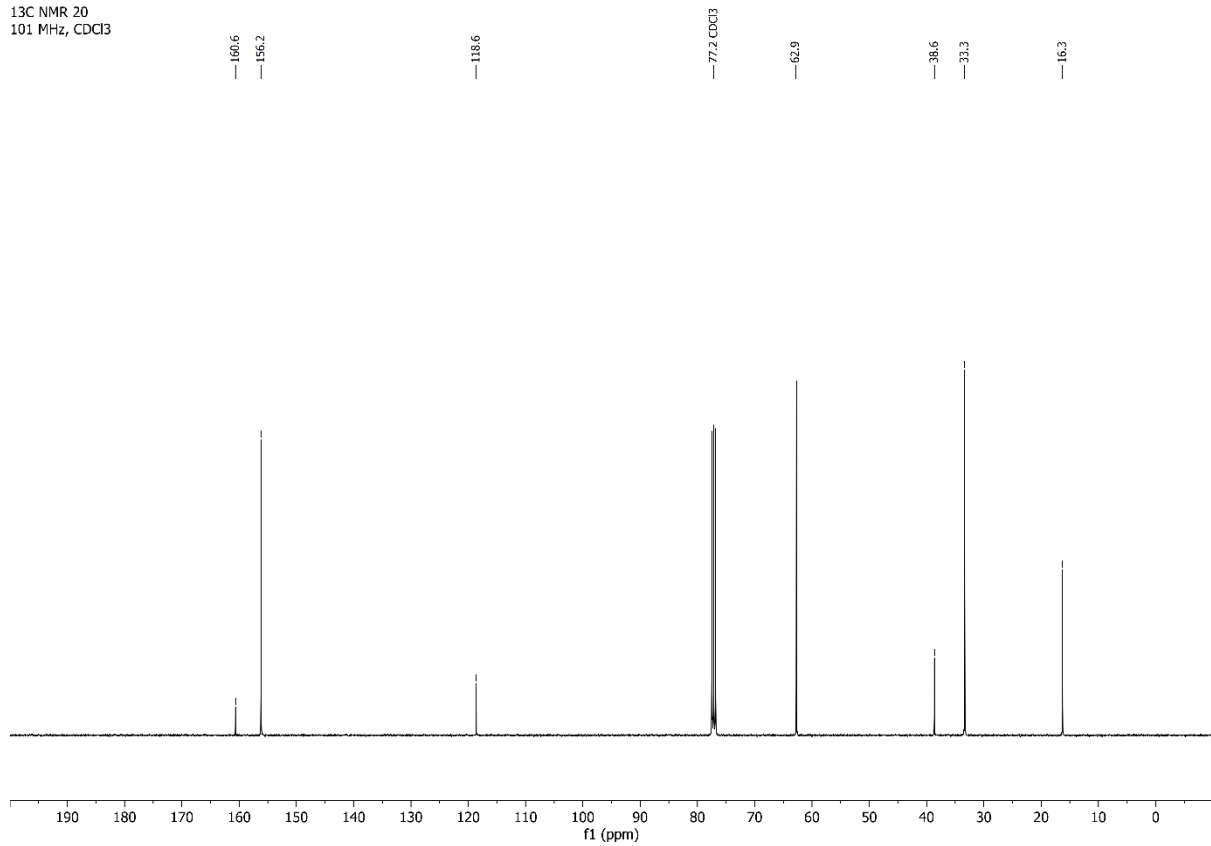
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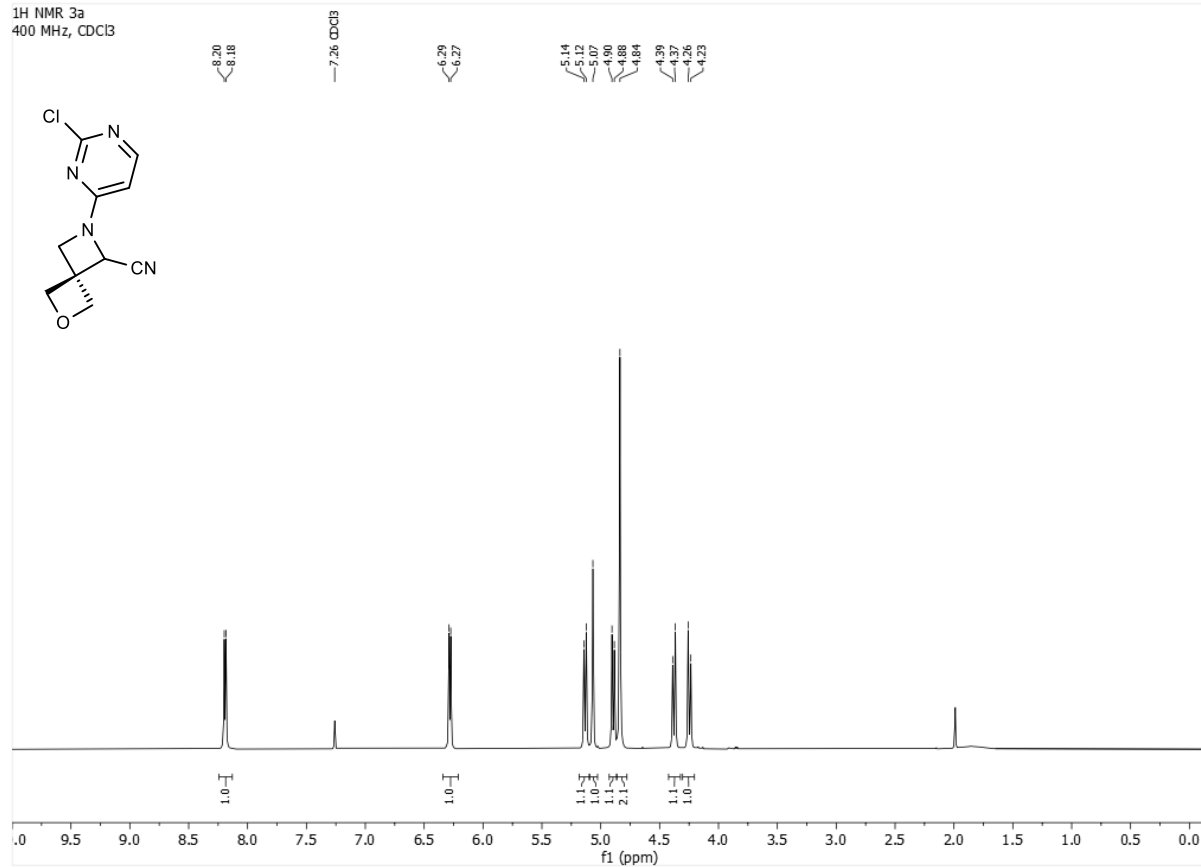
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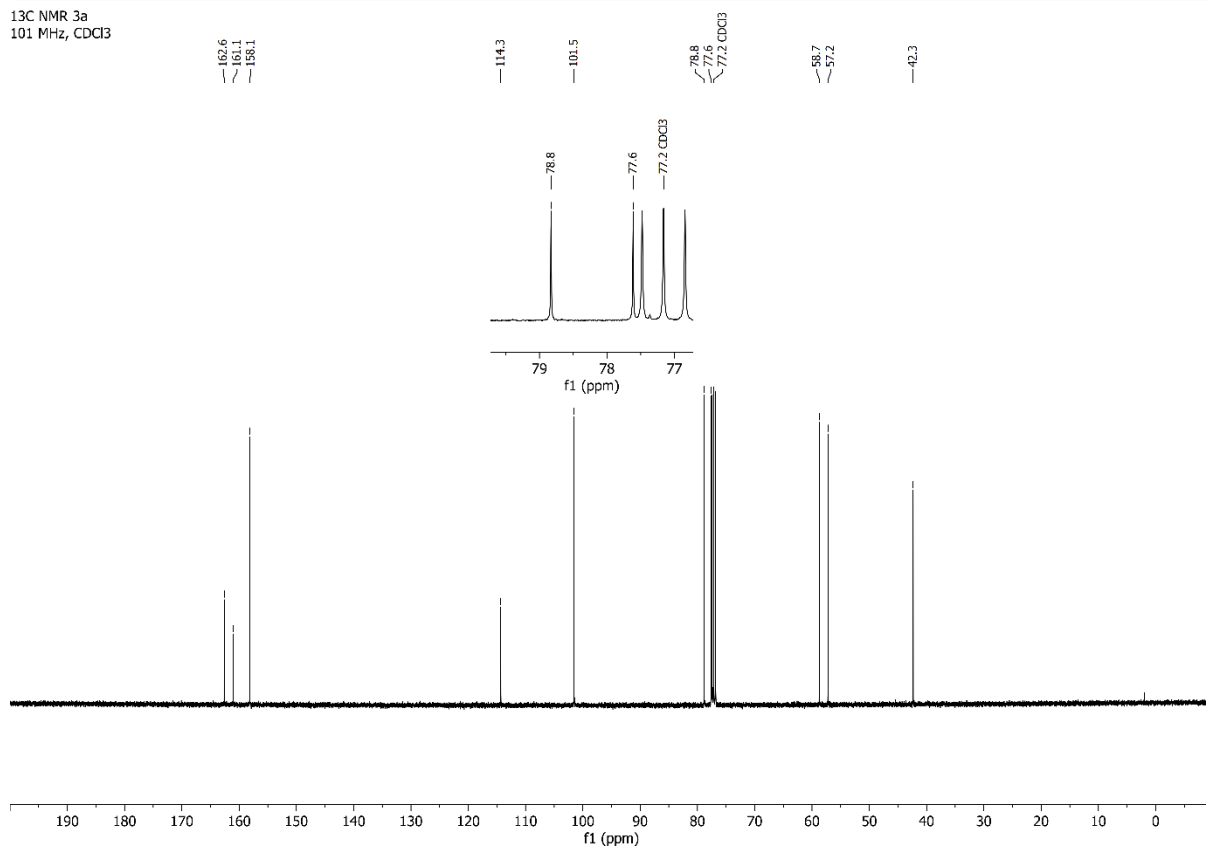
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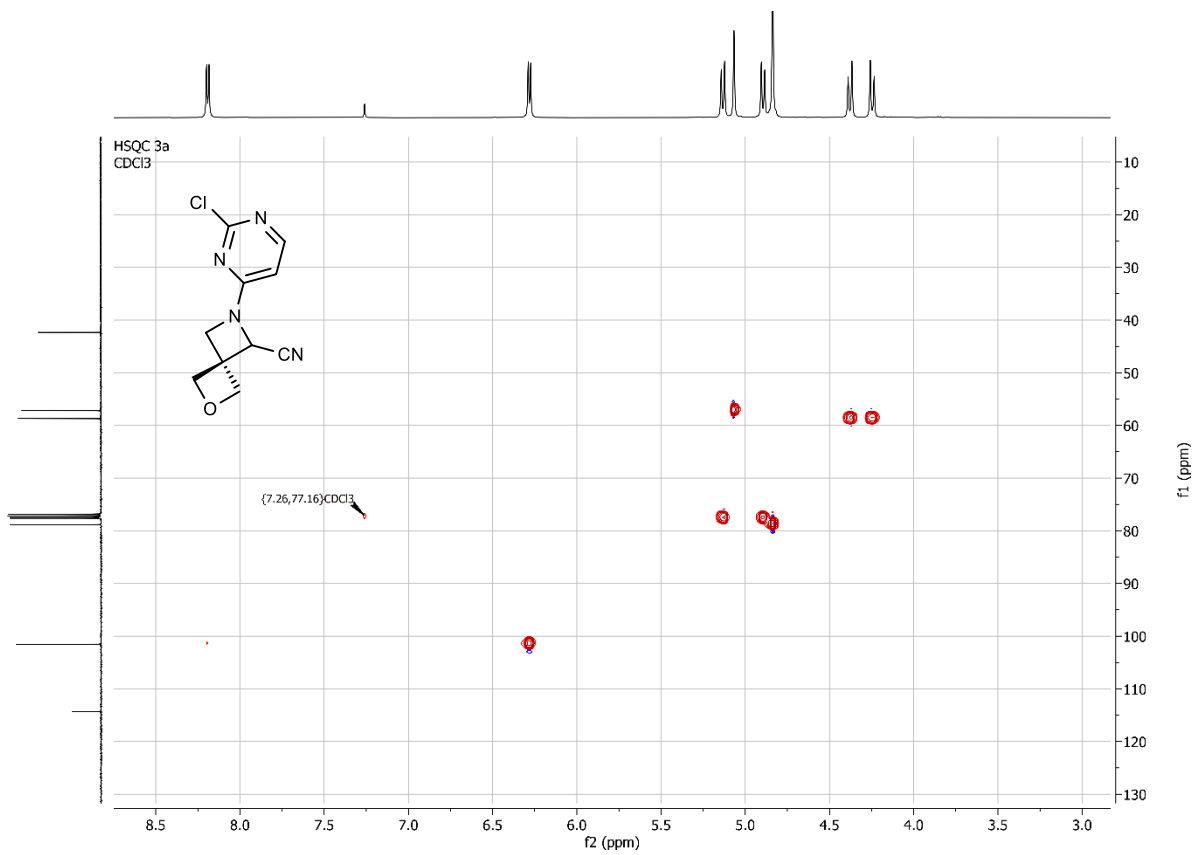


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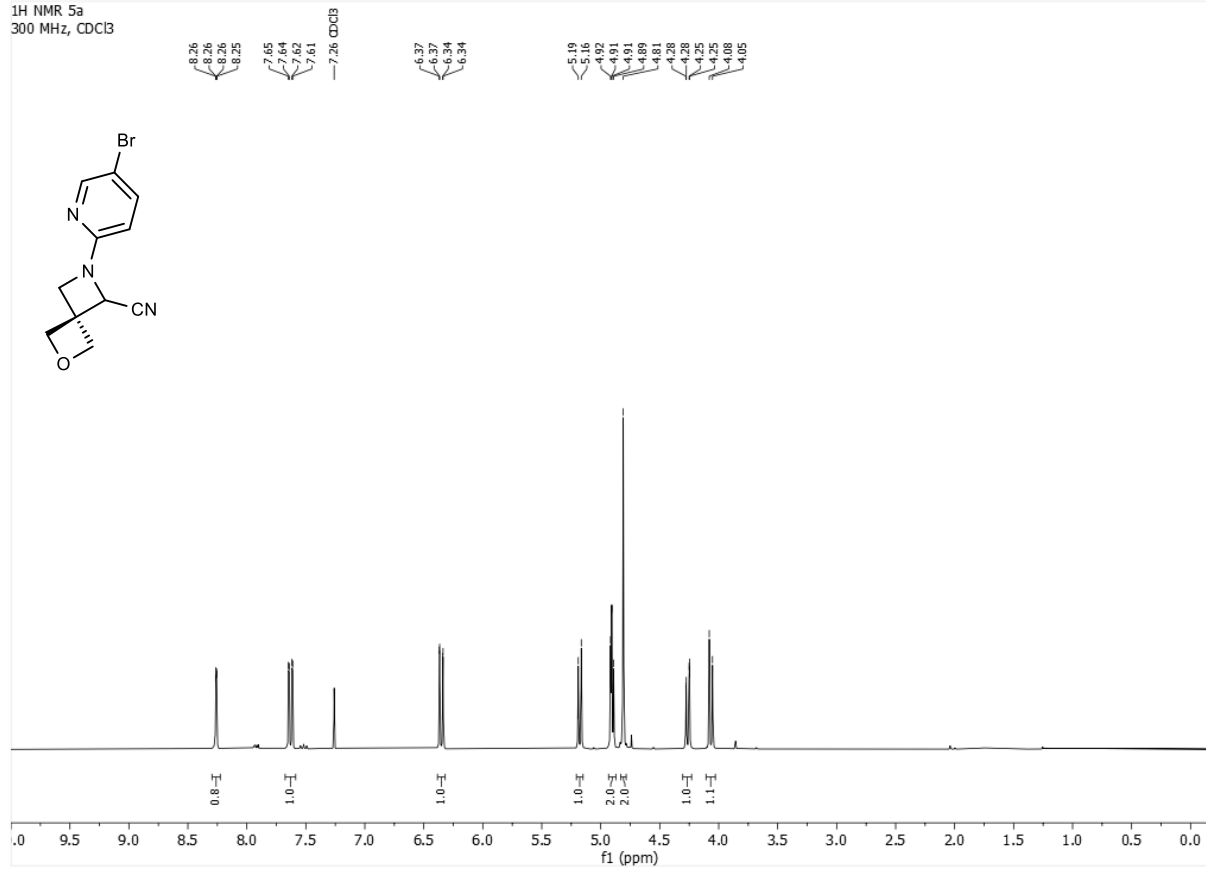


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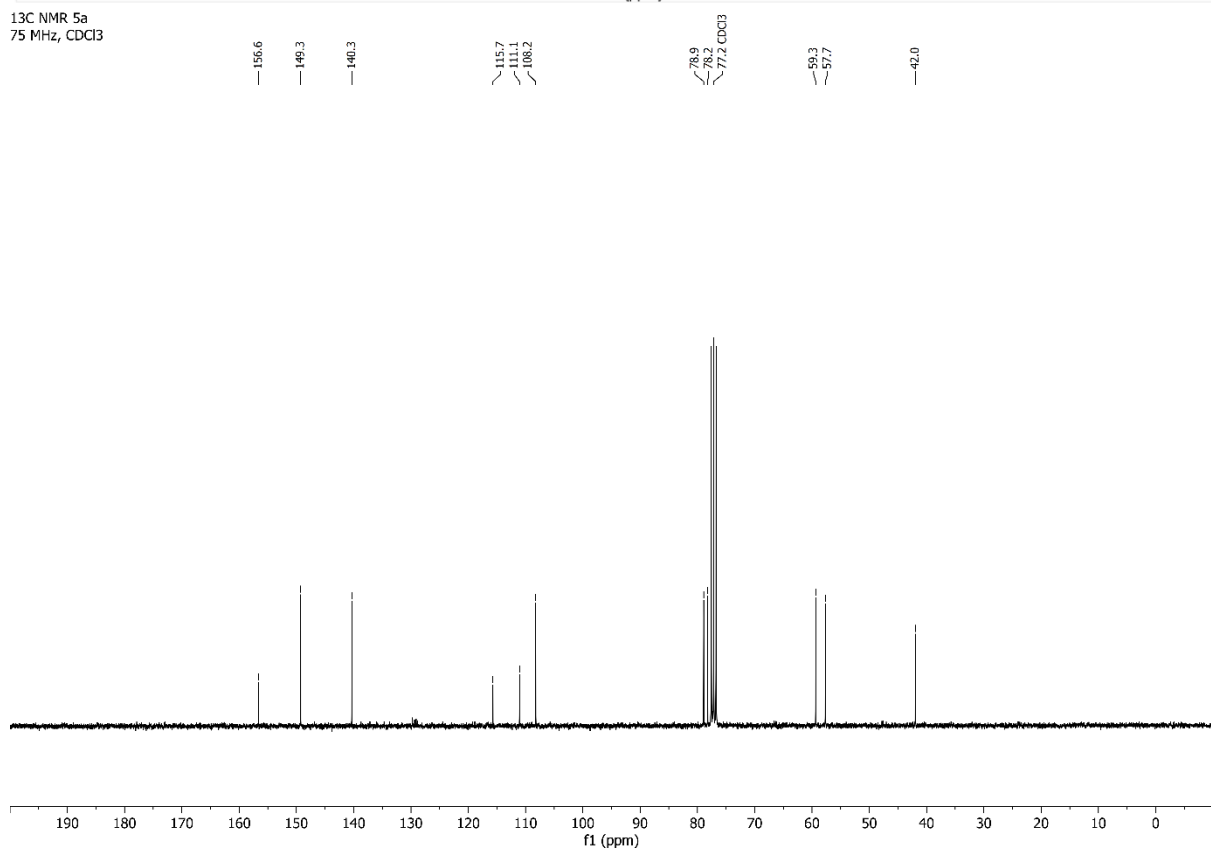




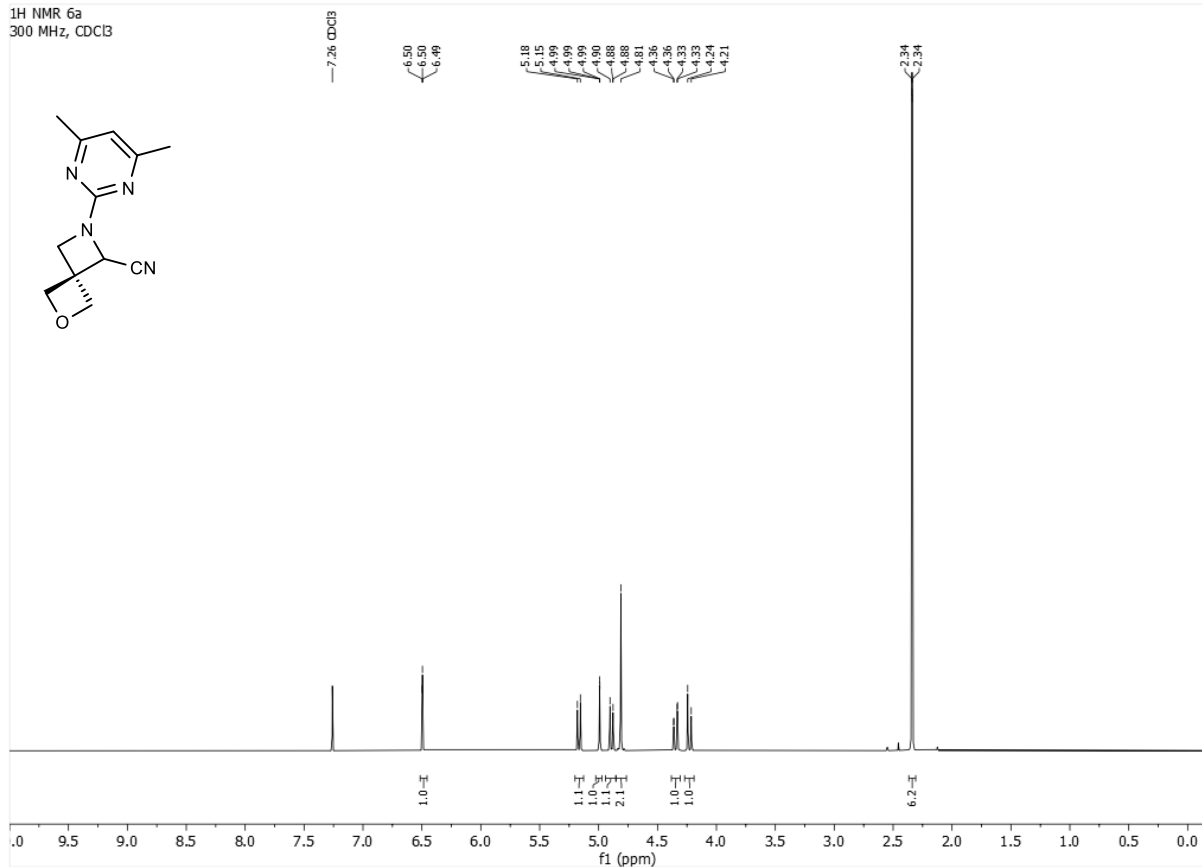
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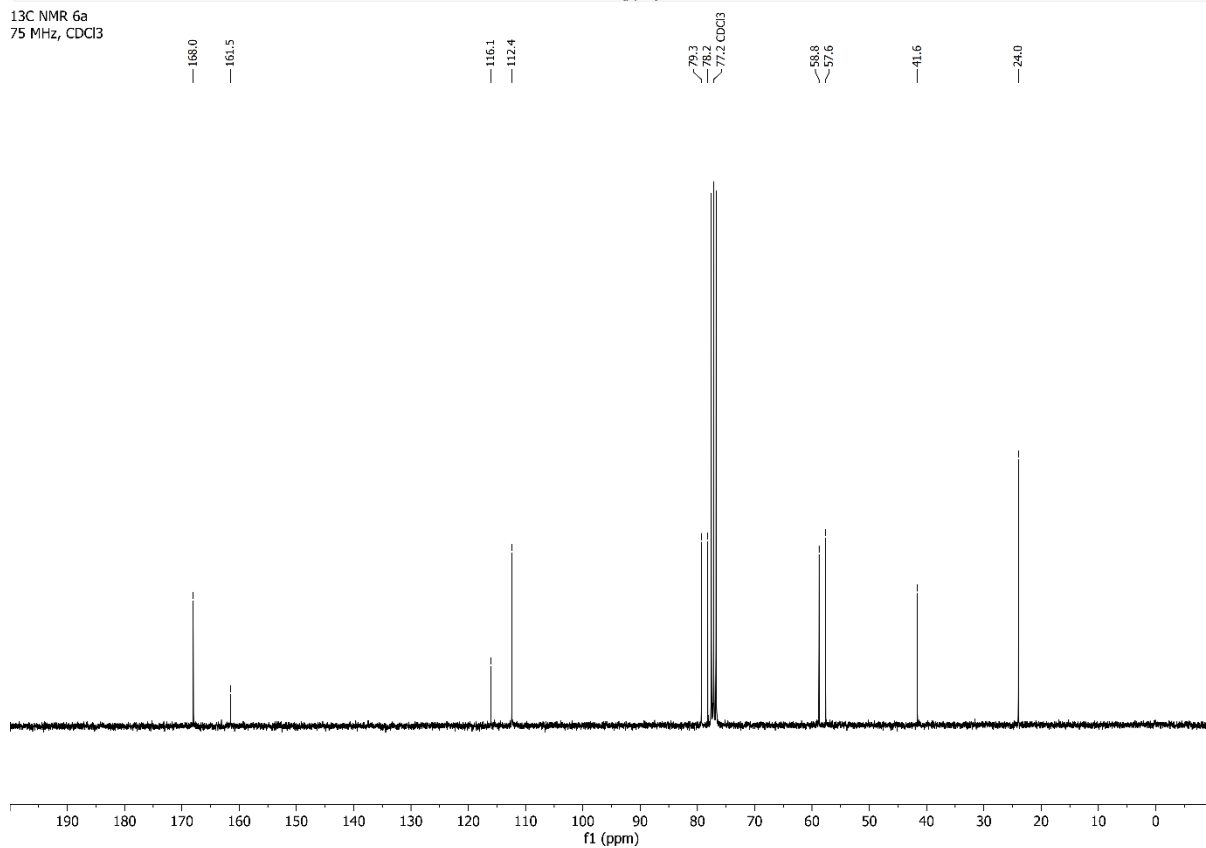
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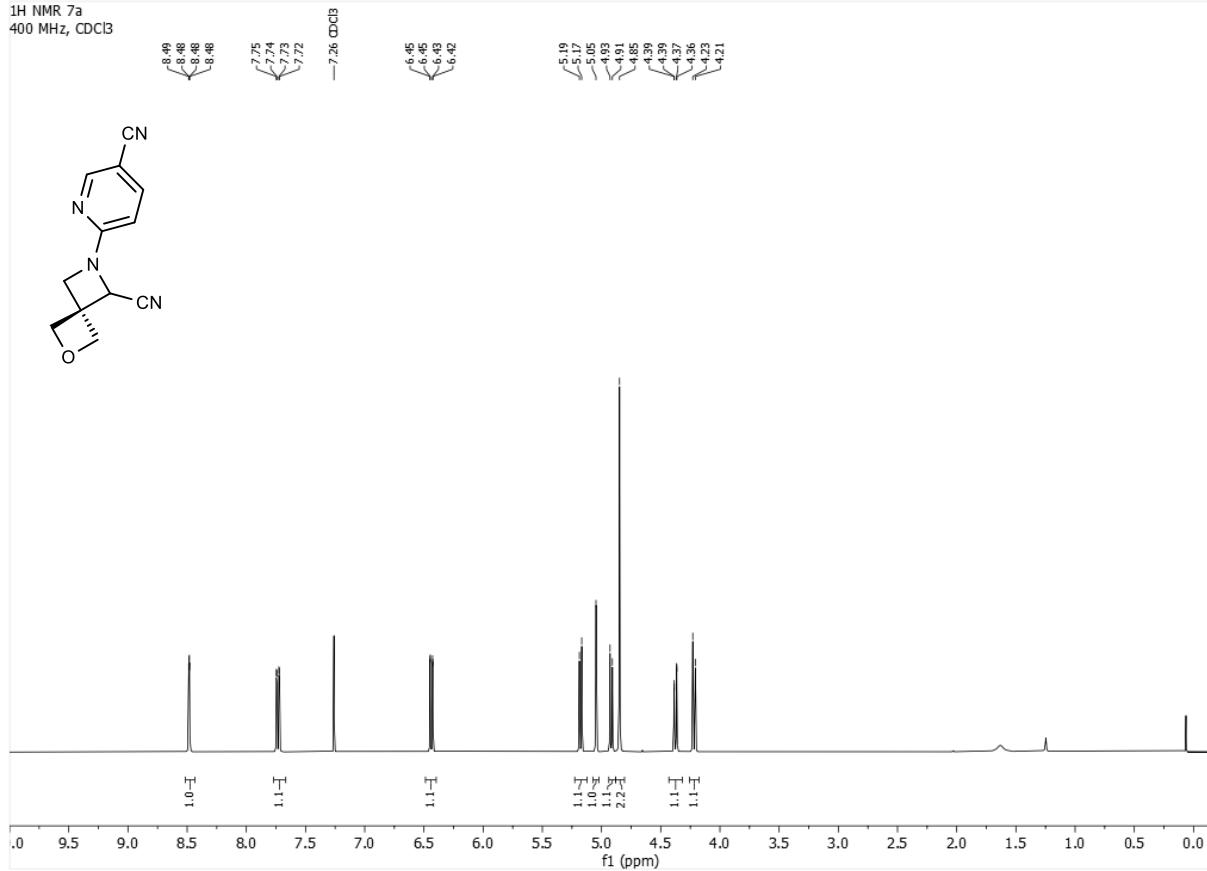
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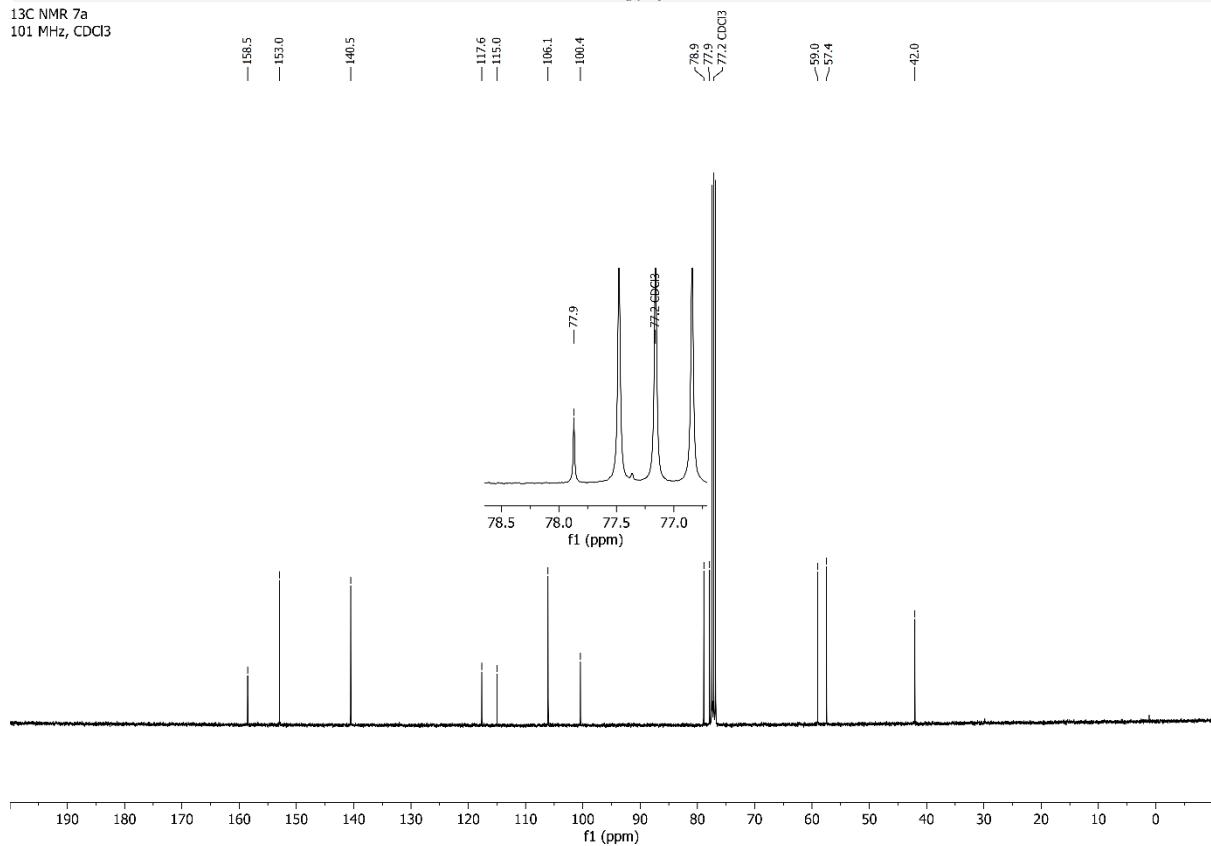
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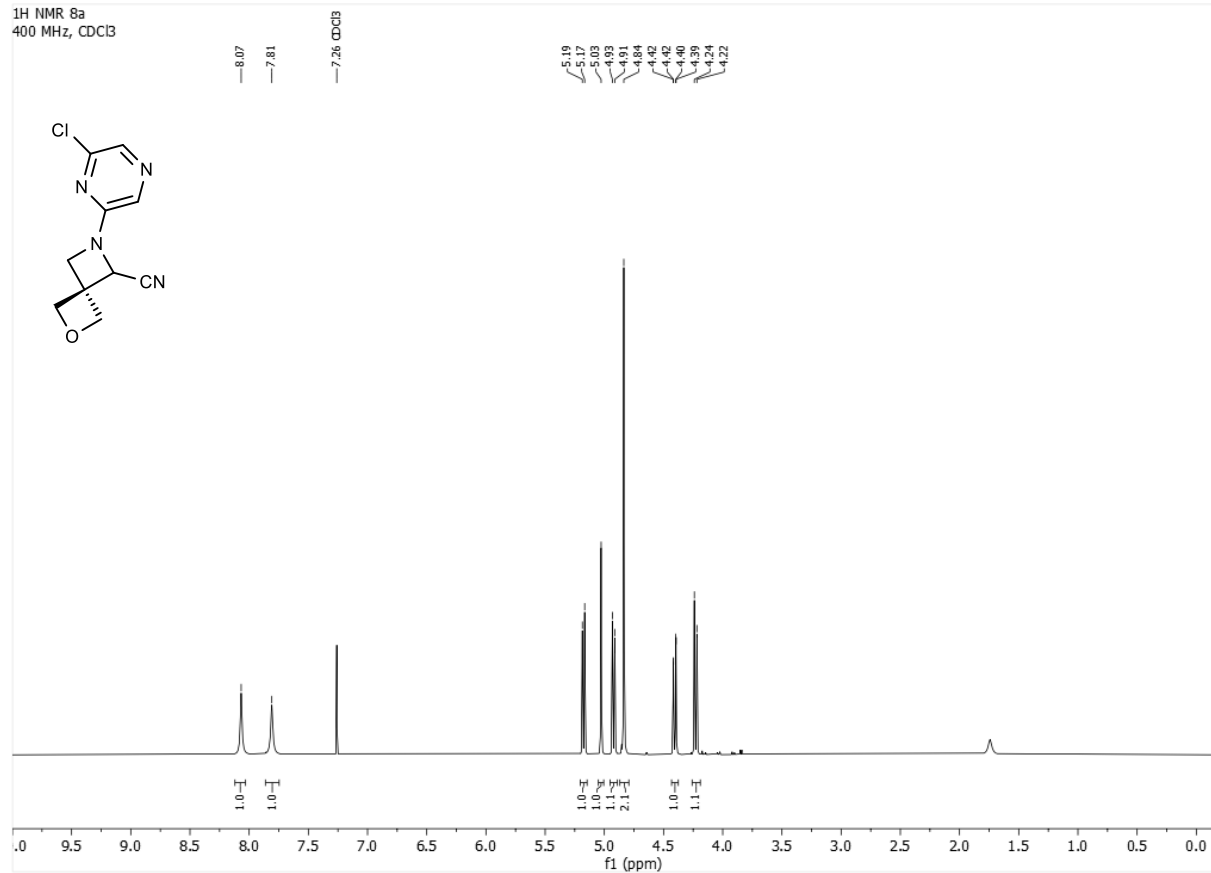
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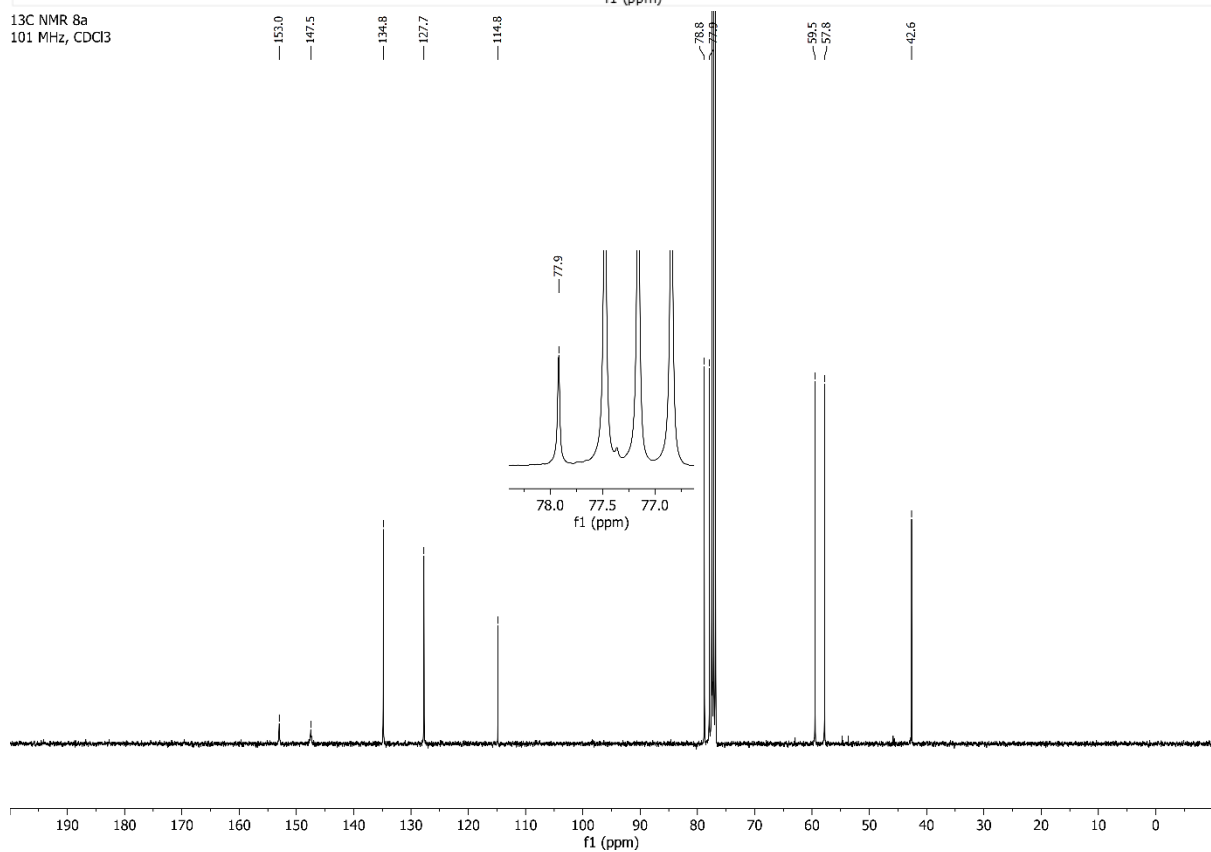
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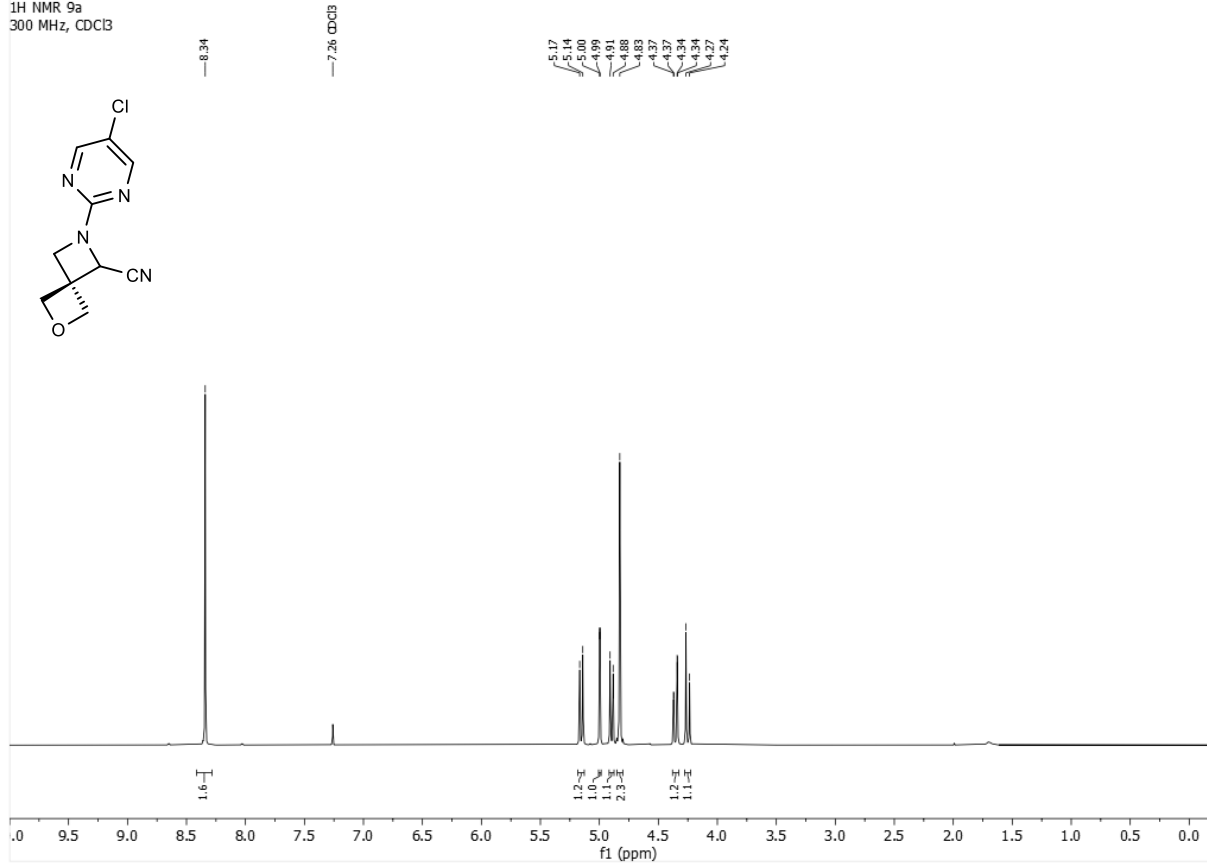
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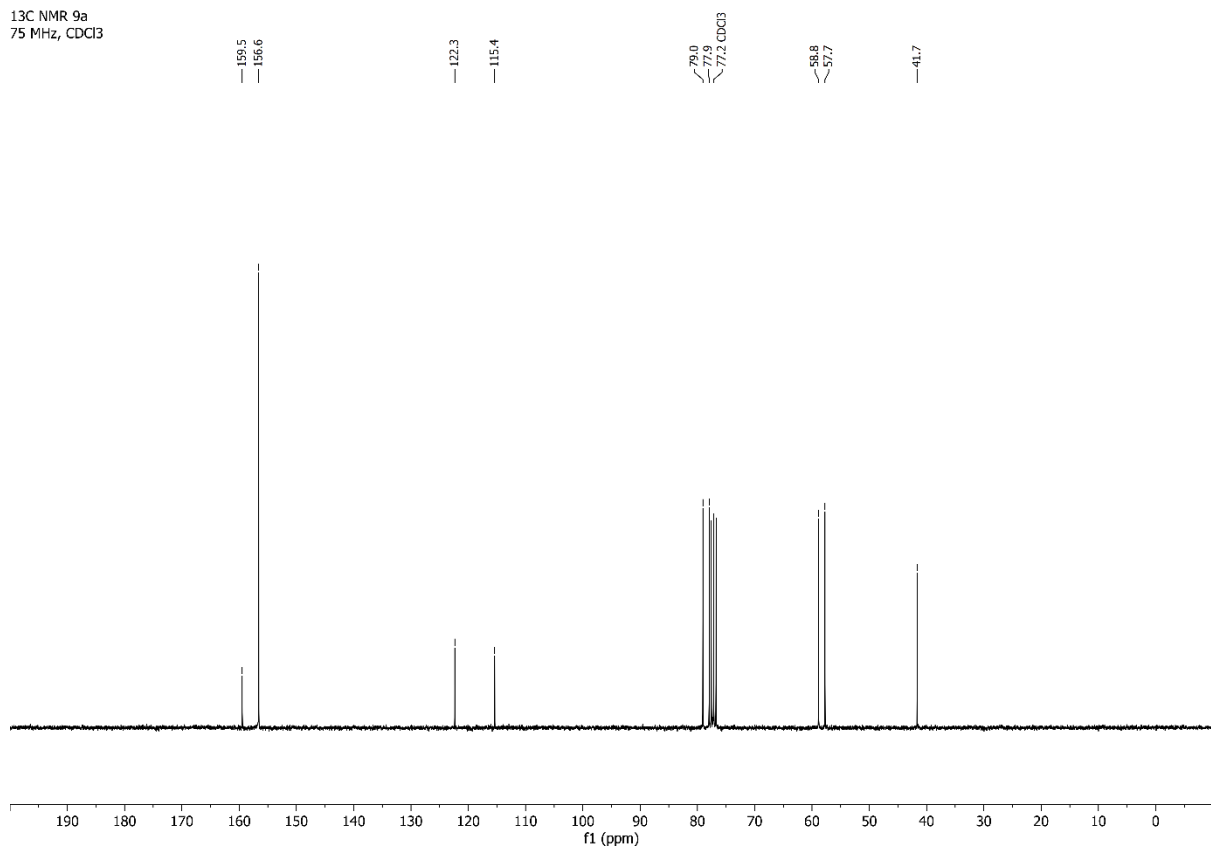
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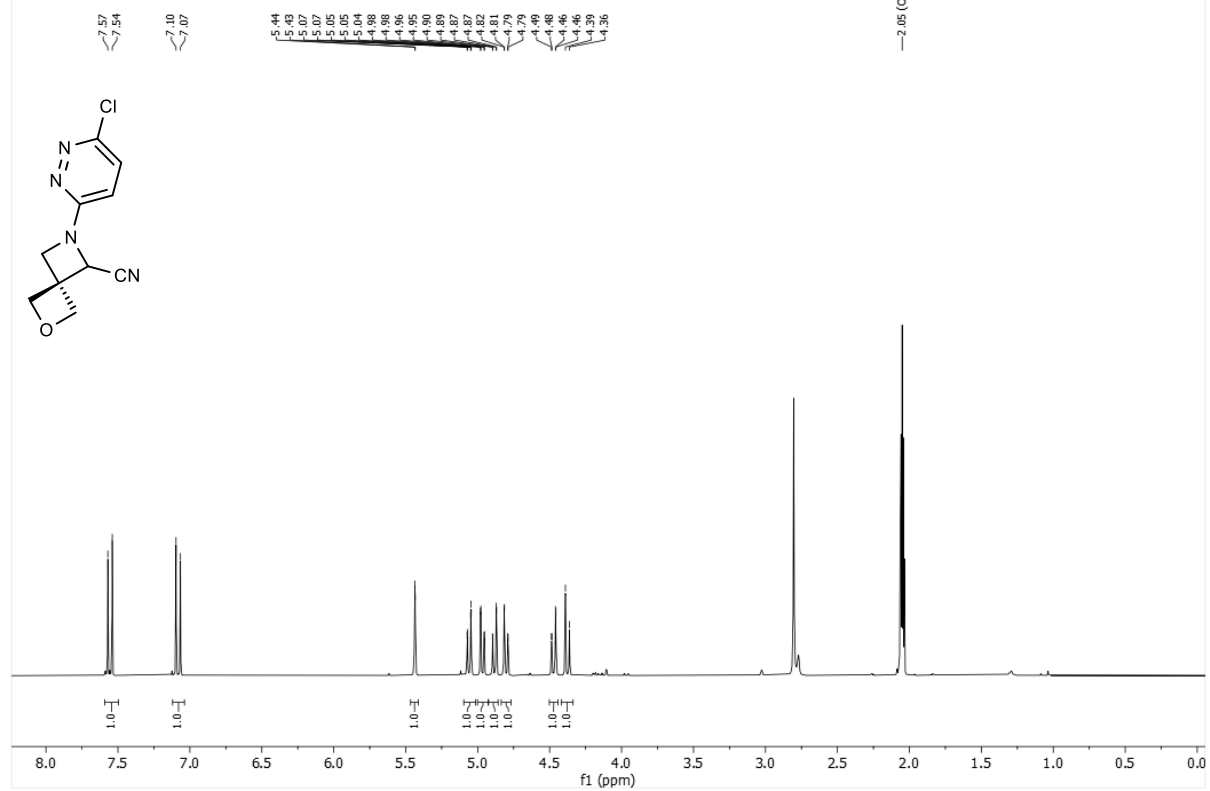
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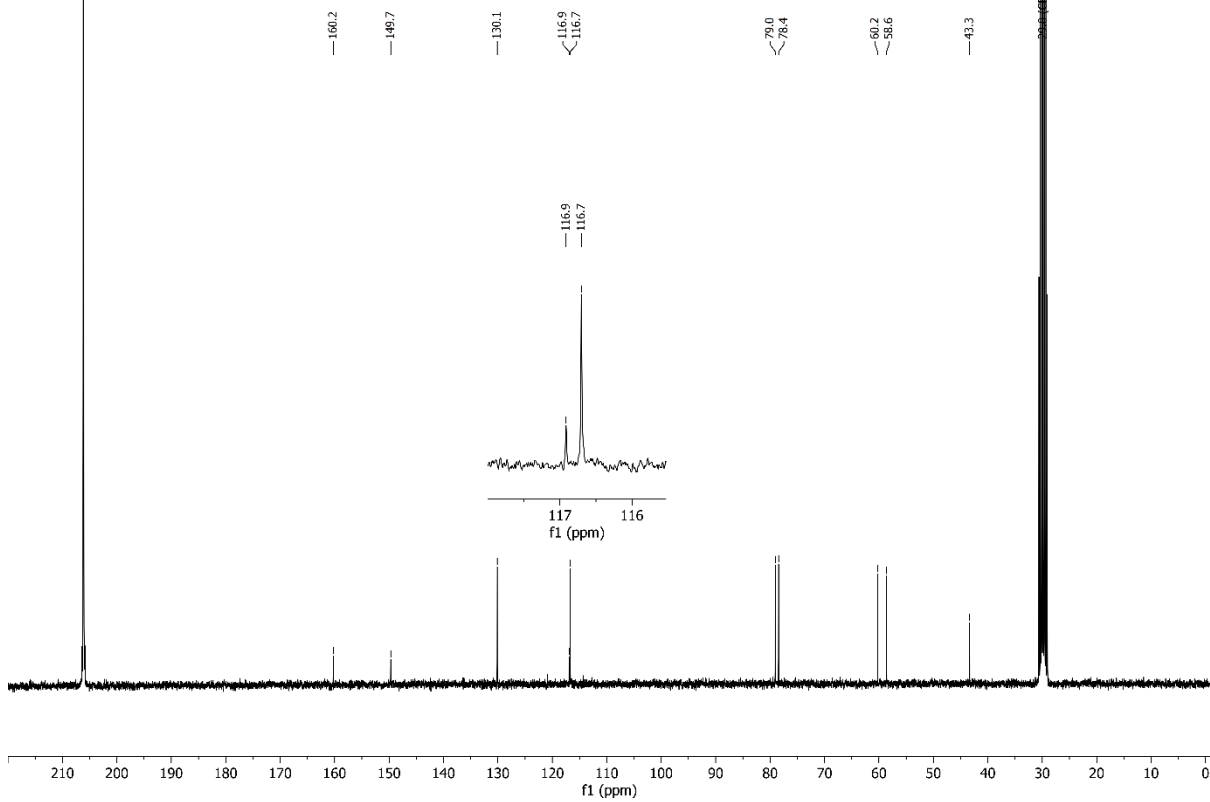
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75 MHz, CDCl₃

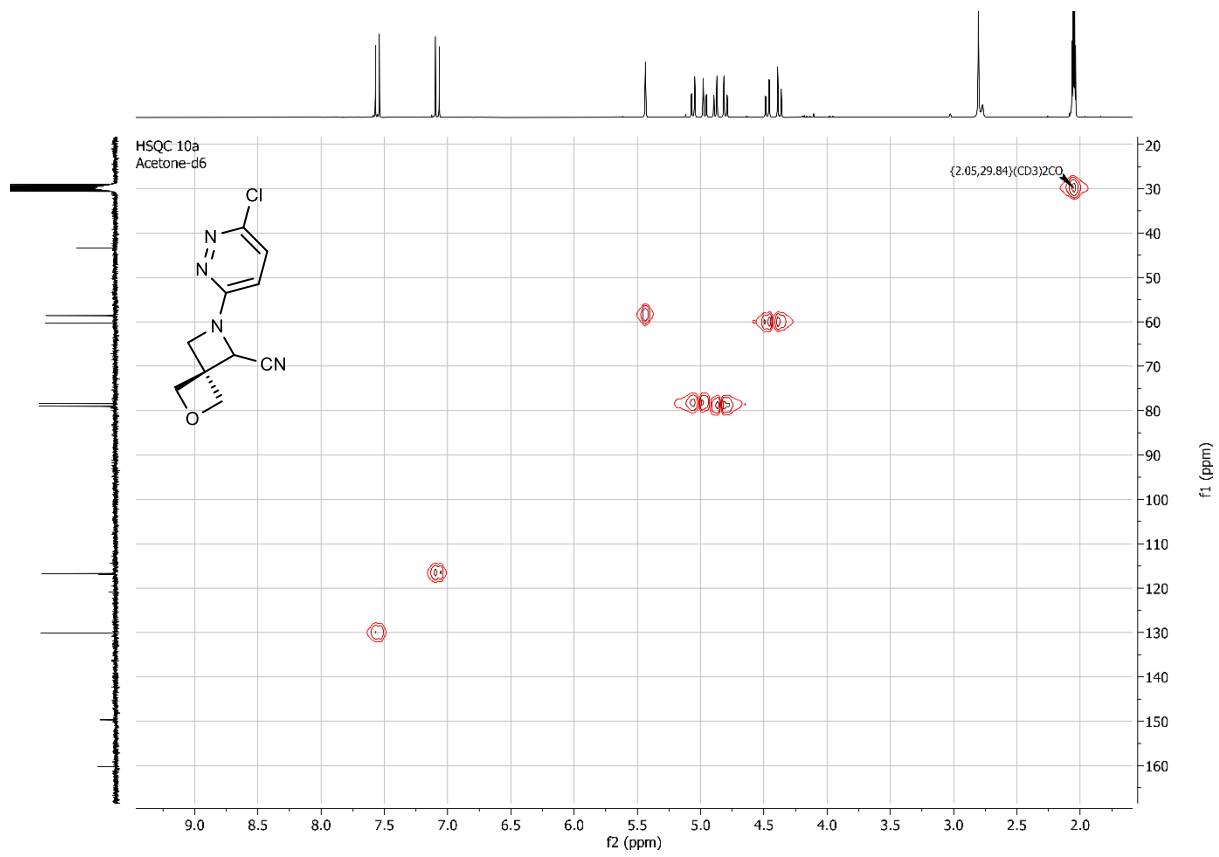


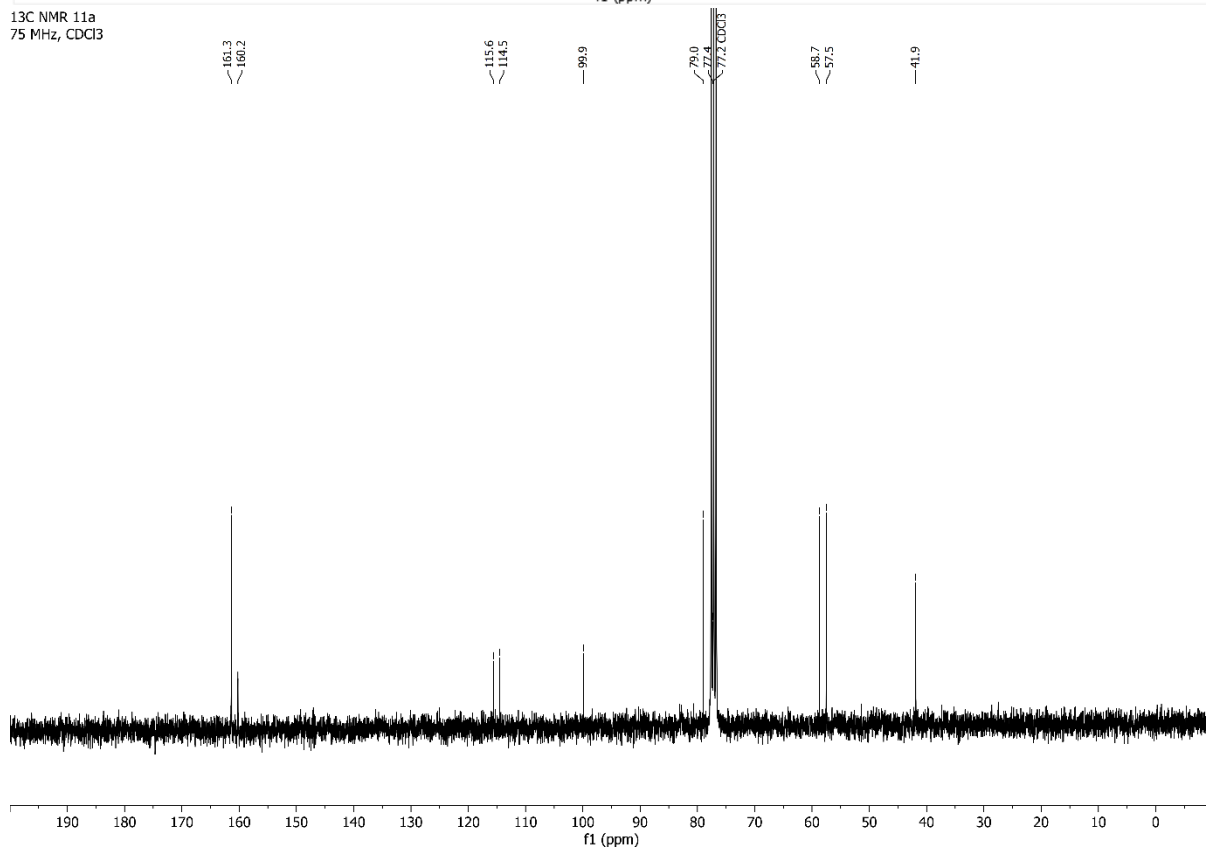
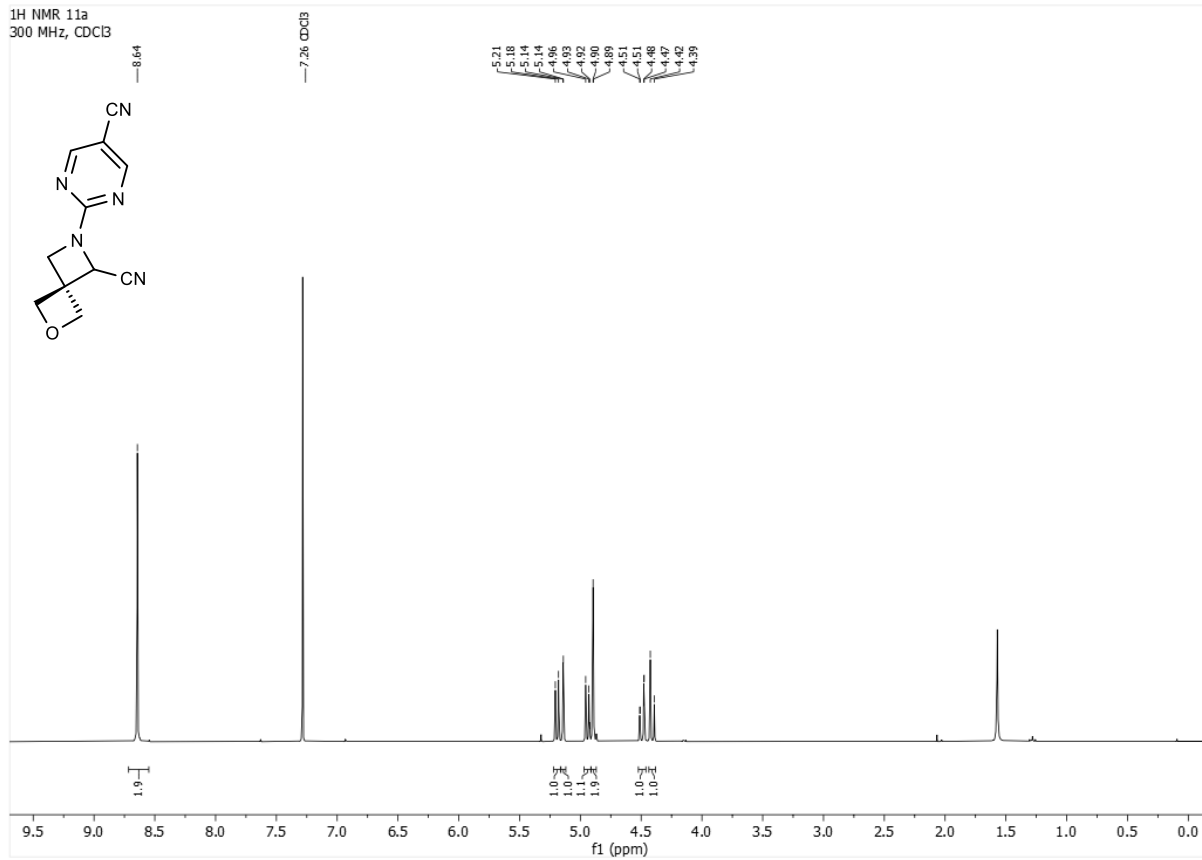
1H NMR 10a
300 MHz, Acetone-d6



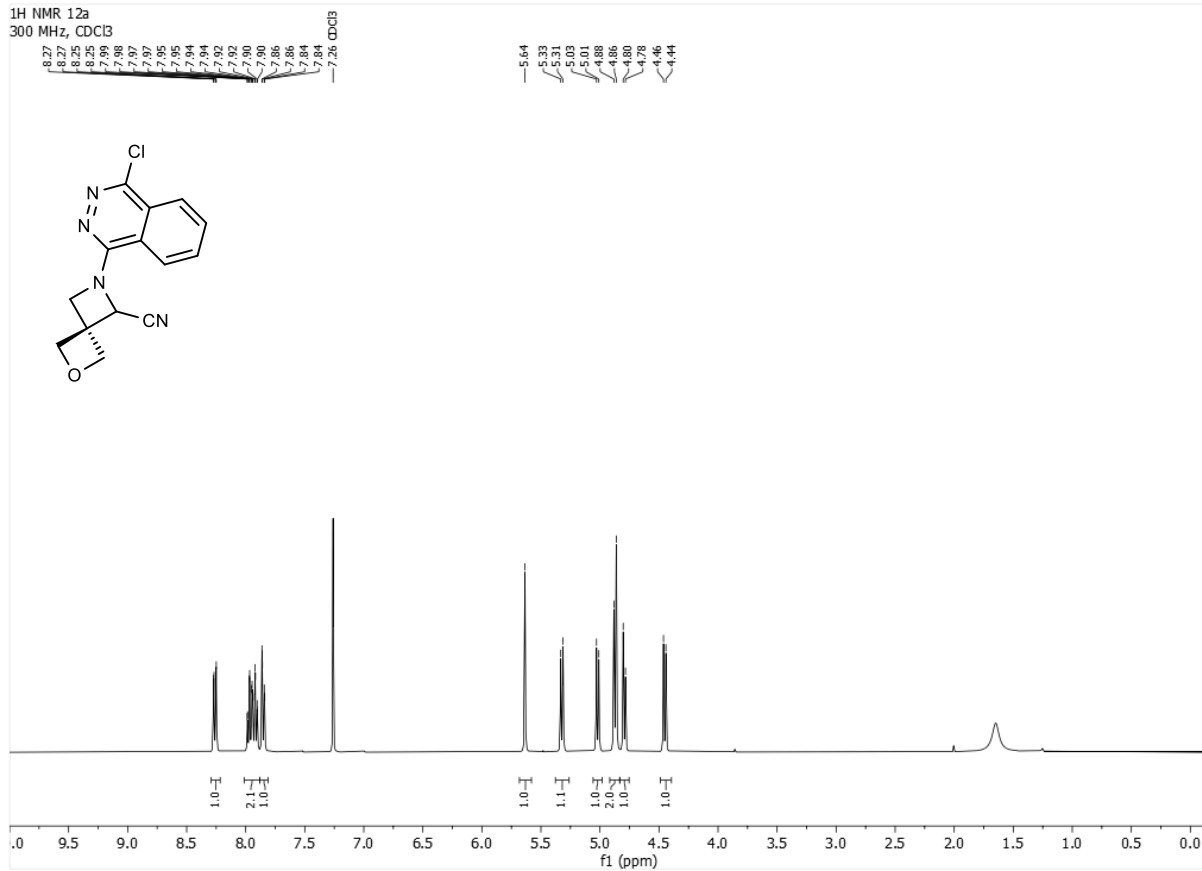
13C NMR 10a
75 MHz, Acetone-d6



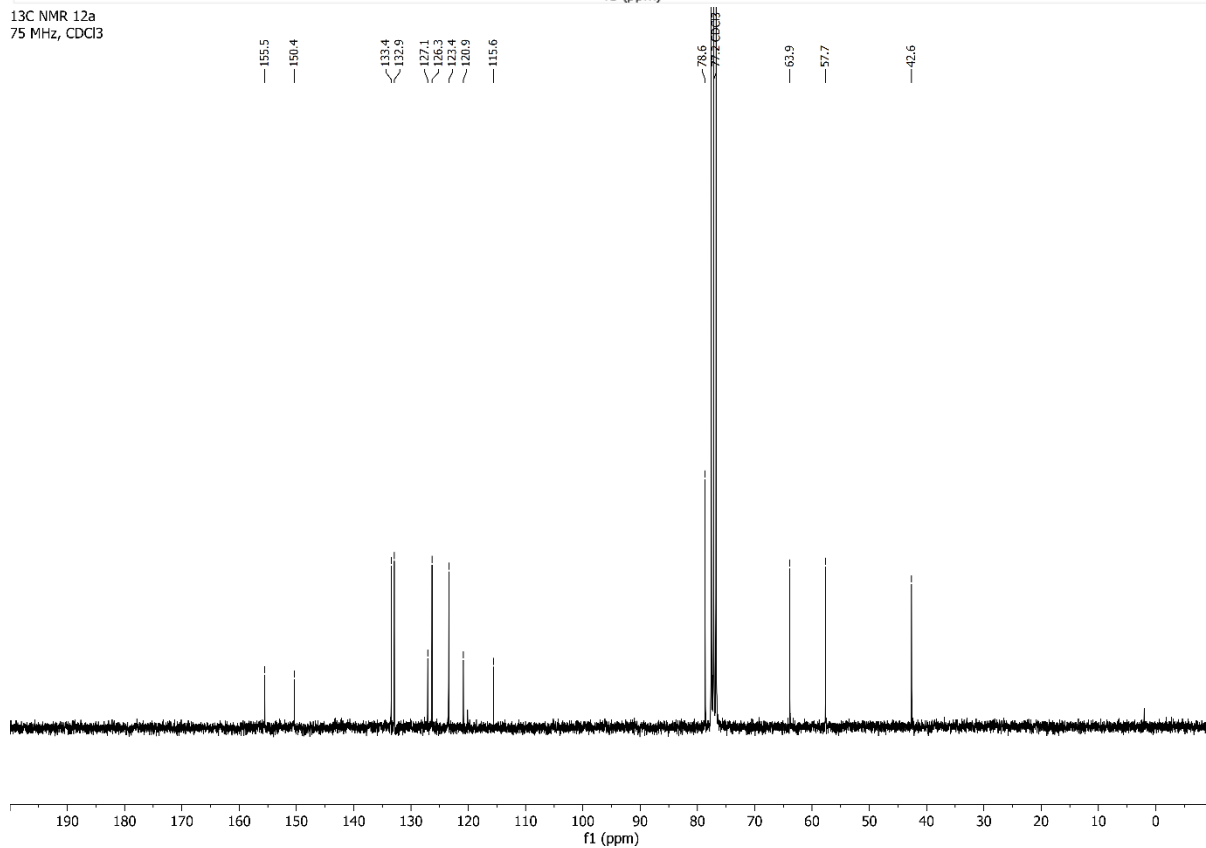


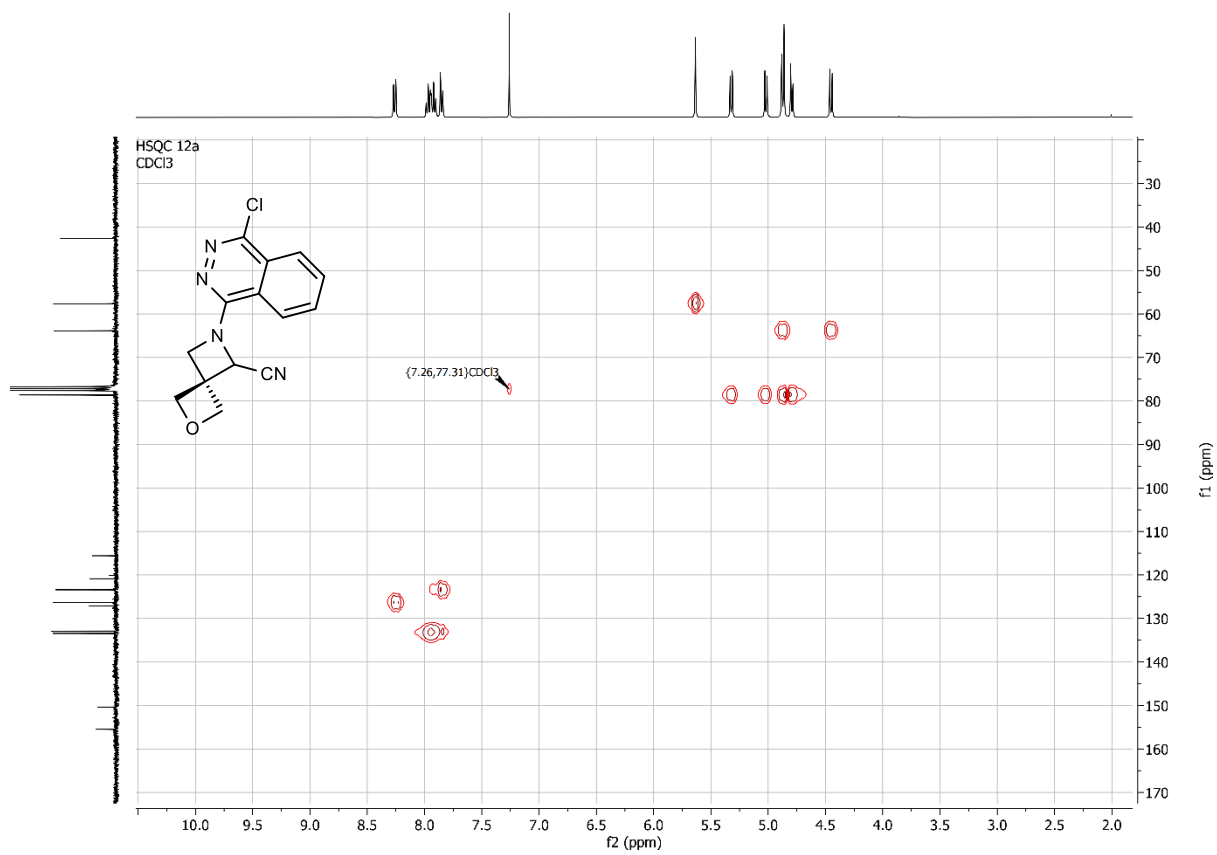


¹H NMR 12a
300 MHz, CDCl₃

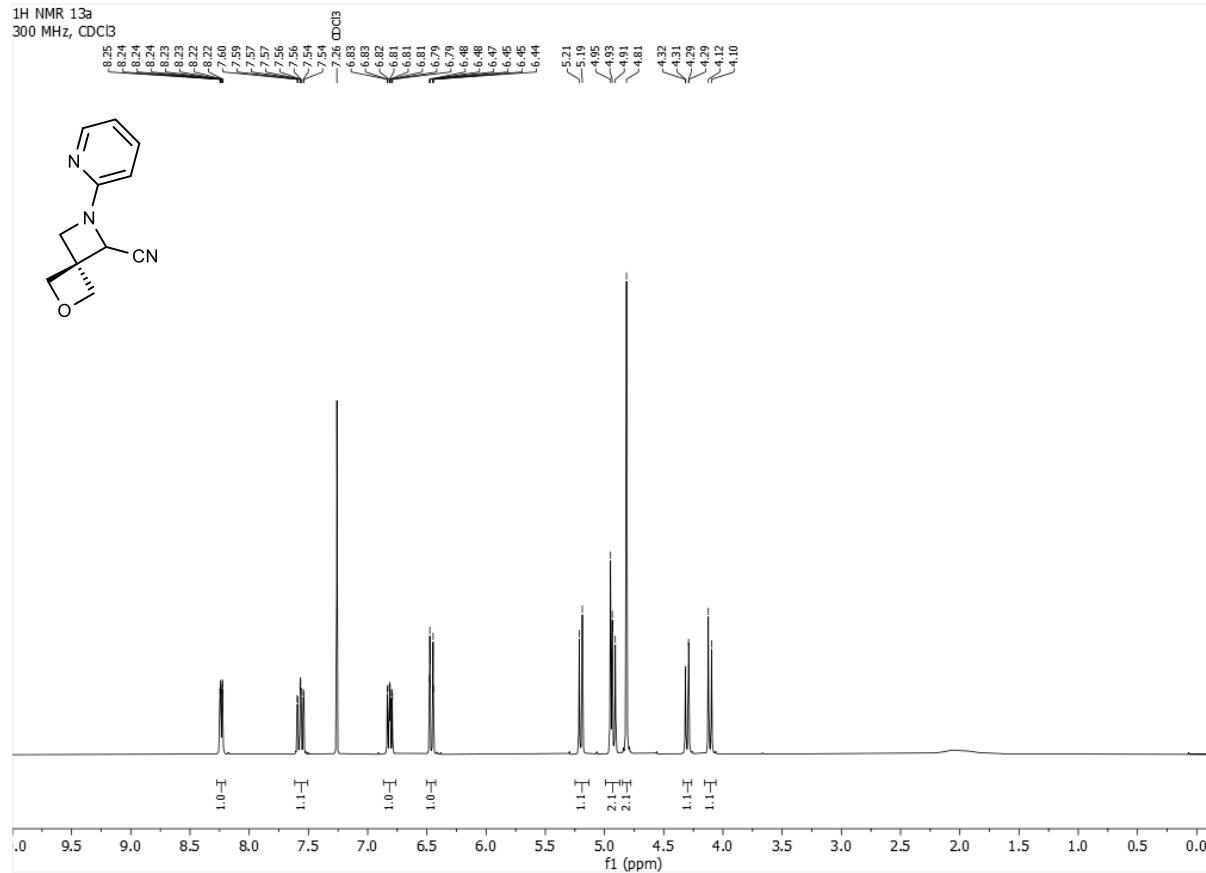


¹³C NMR 12a
75 MHz, CDCl₃

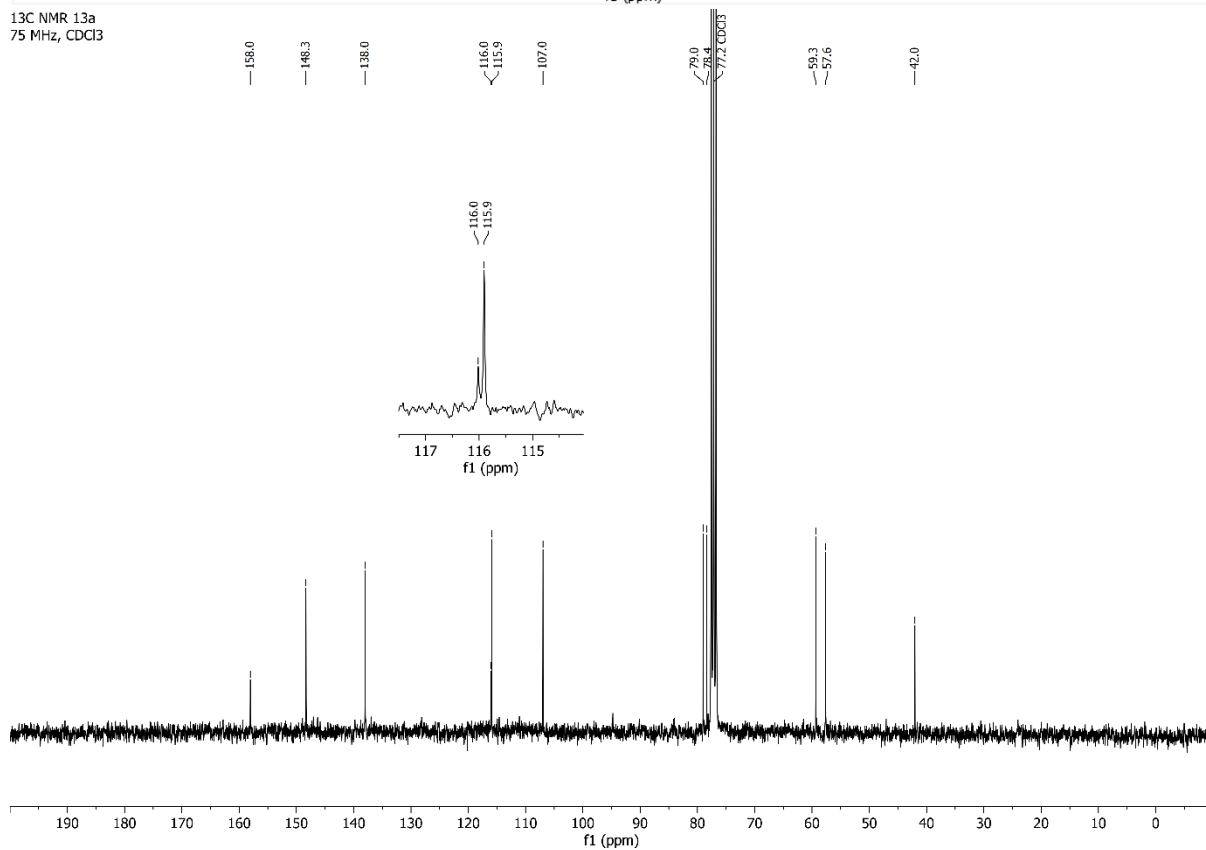




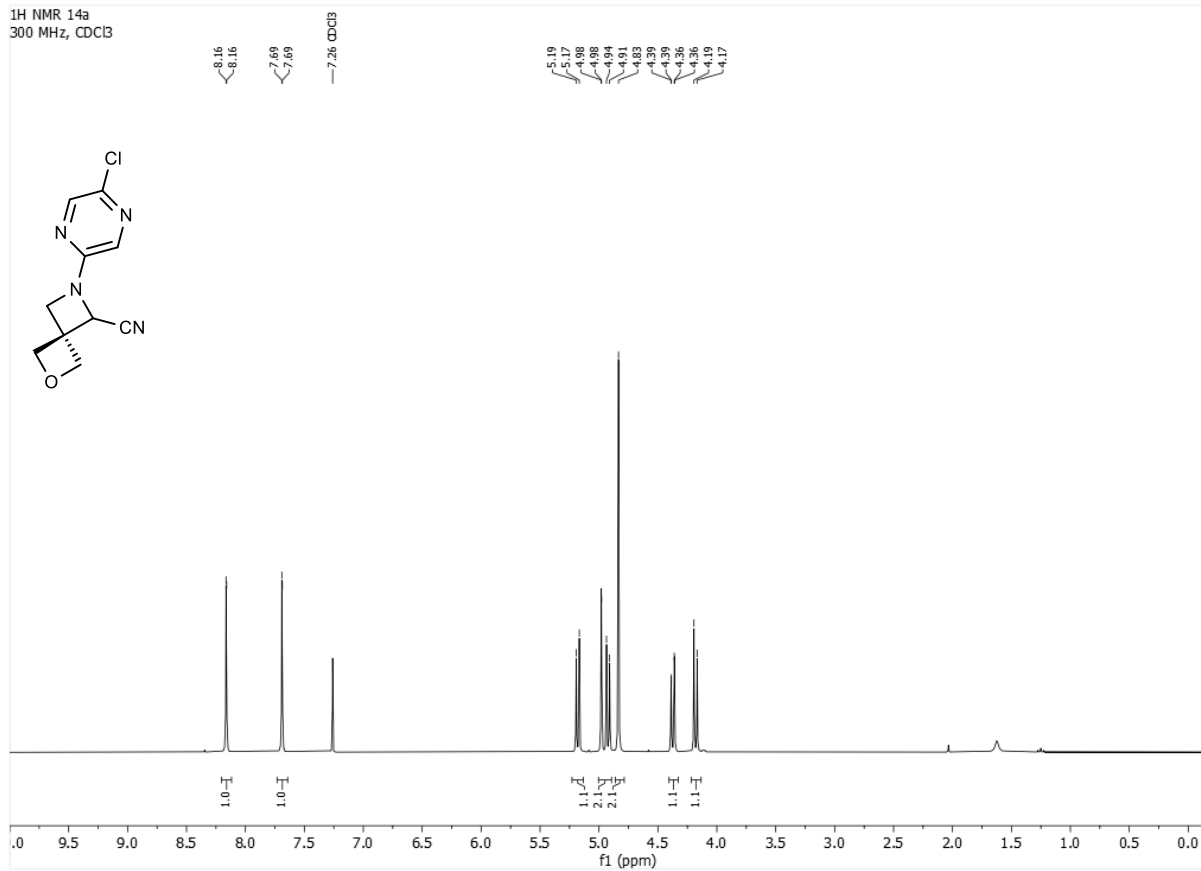
¹H NMR 13a
300 MHz, CDCl₃



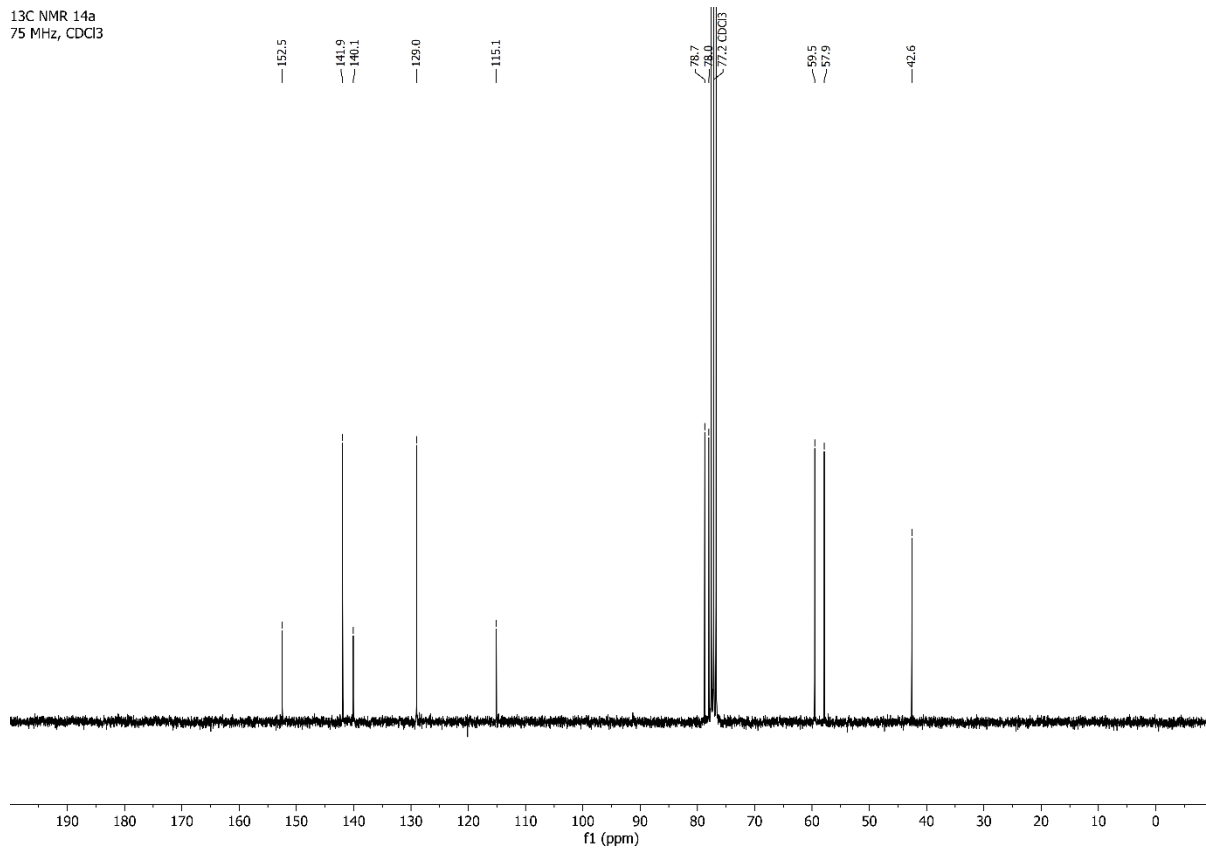
¹³C NMR 13a
75 MHz, CDCl₃



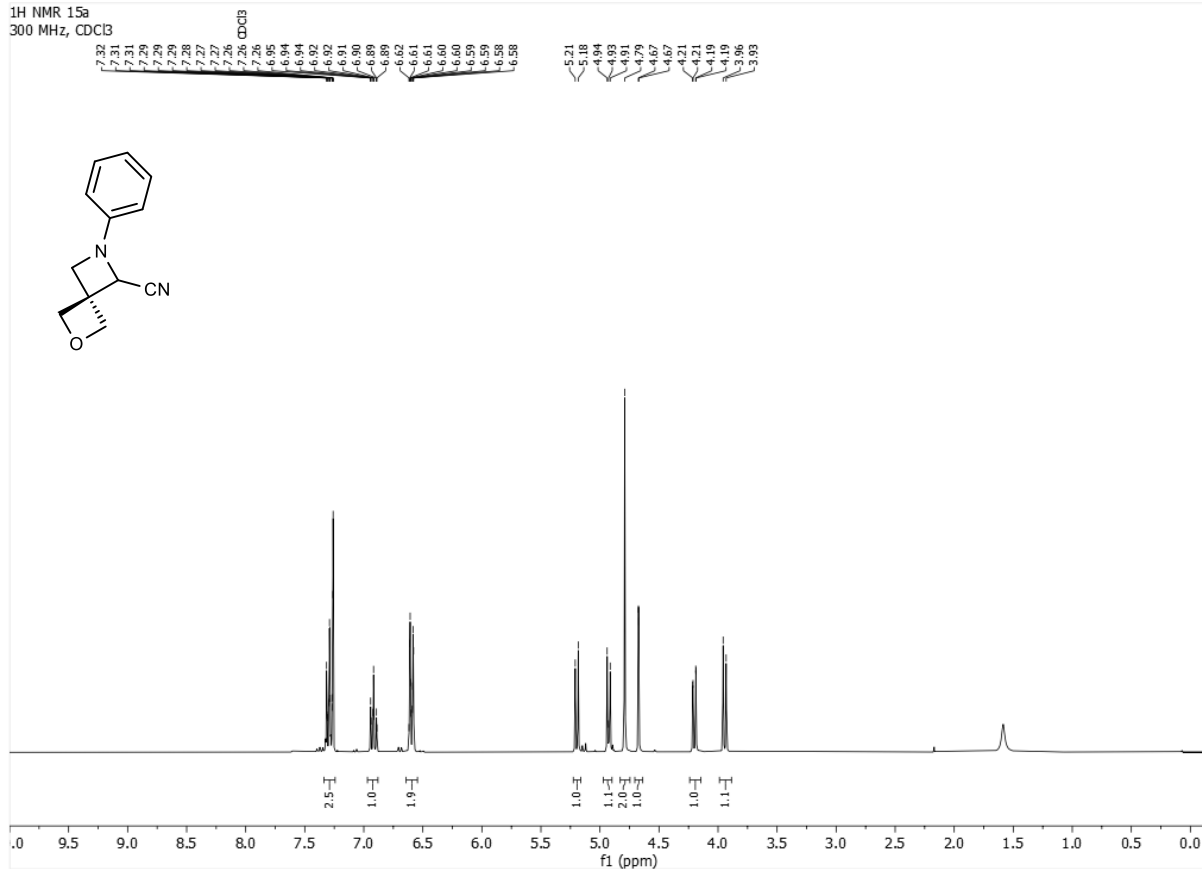
¹H NMR 14a
300 MHz, CDCl₃



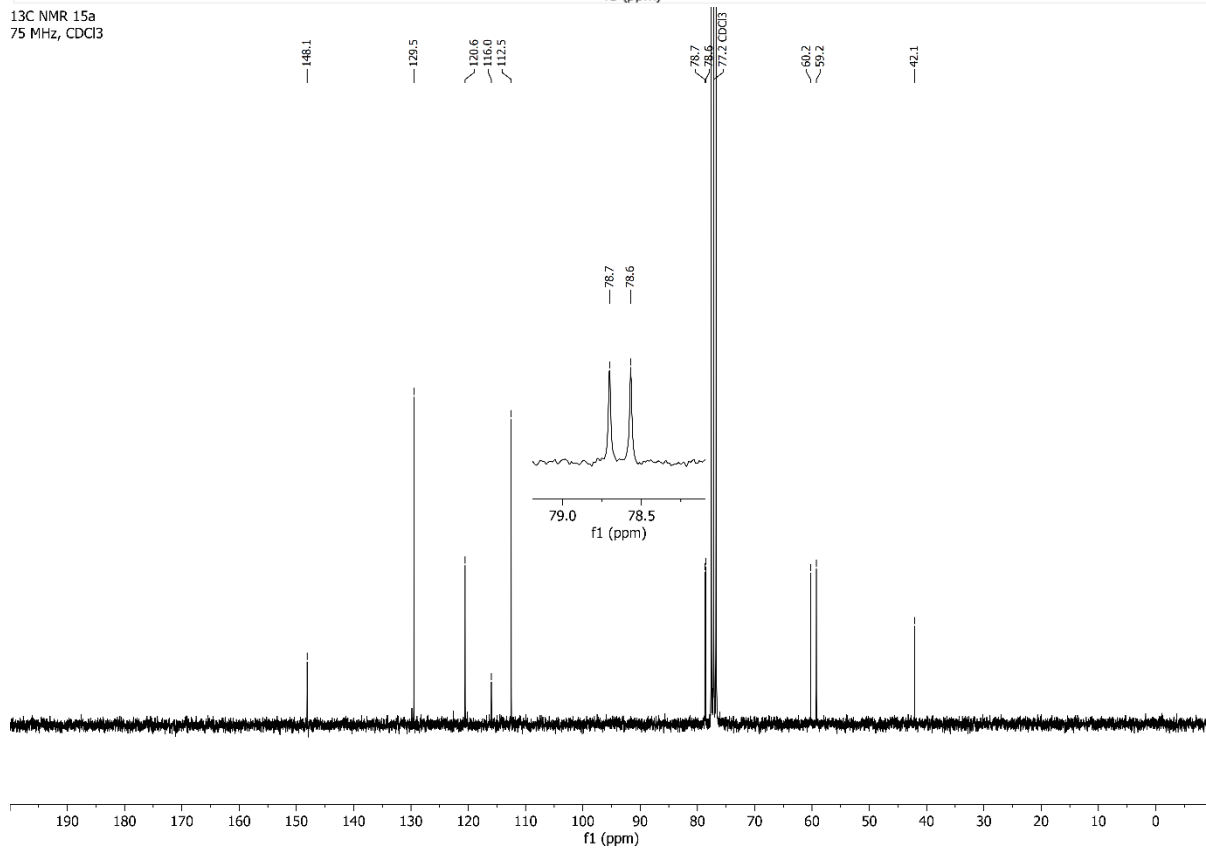
¹³C NMR 14a
75 MHz, CDCl₃



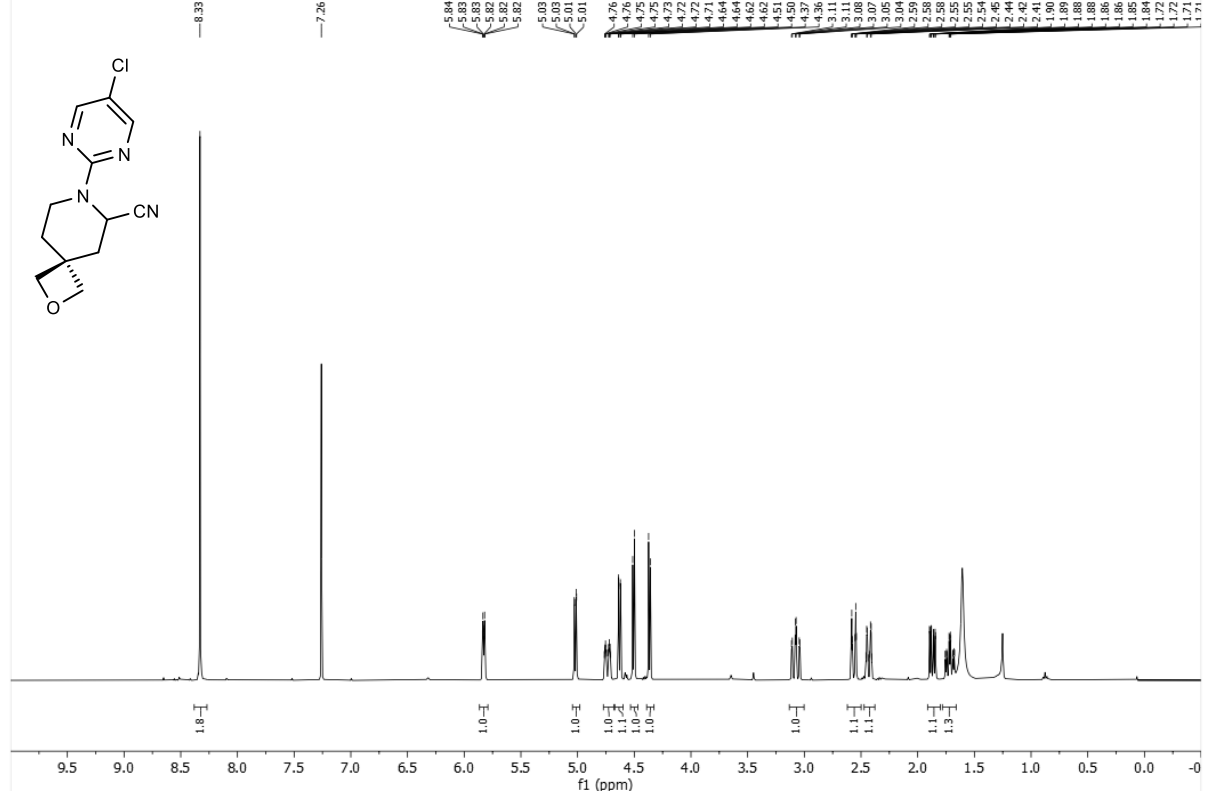
¹H NMR 15a
300 MHz, CDCl₃



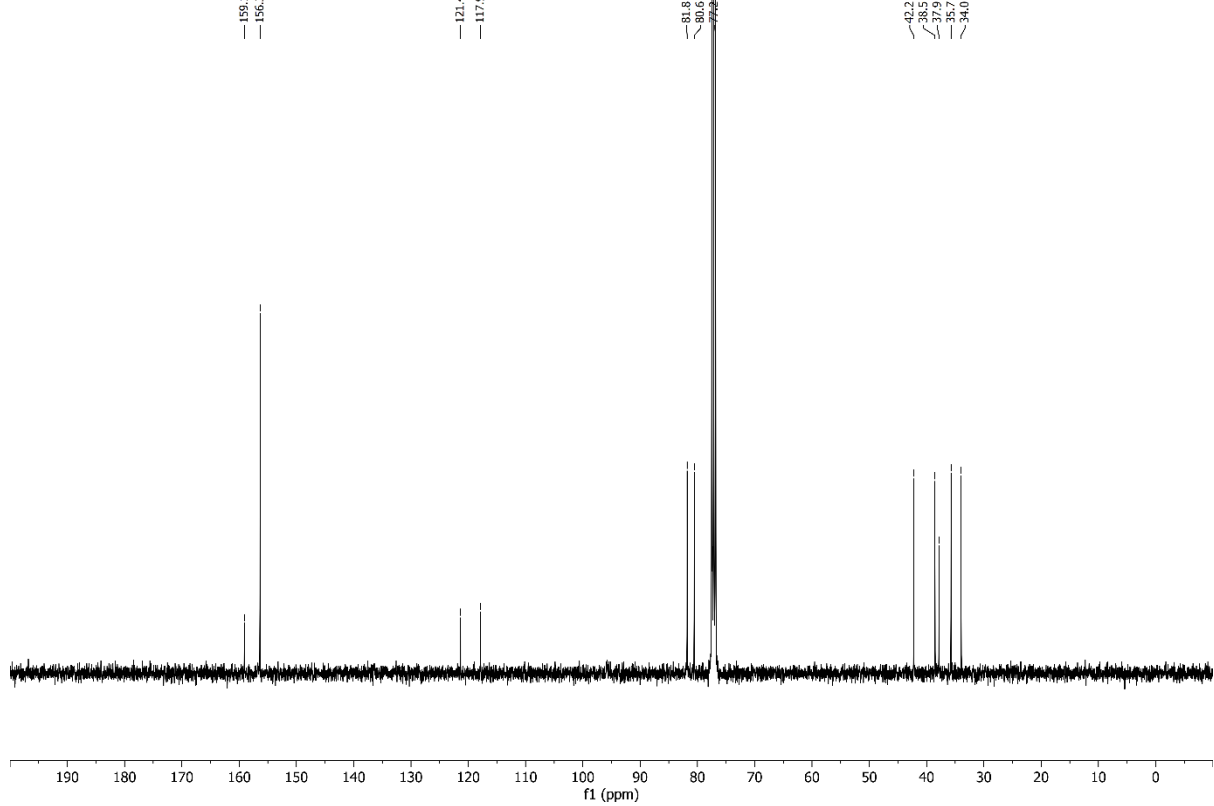
¹³C NMR 15a
75 MHz, CDCl₃

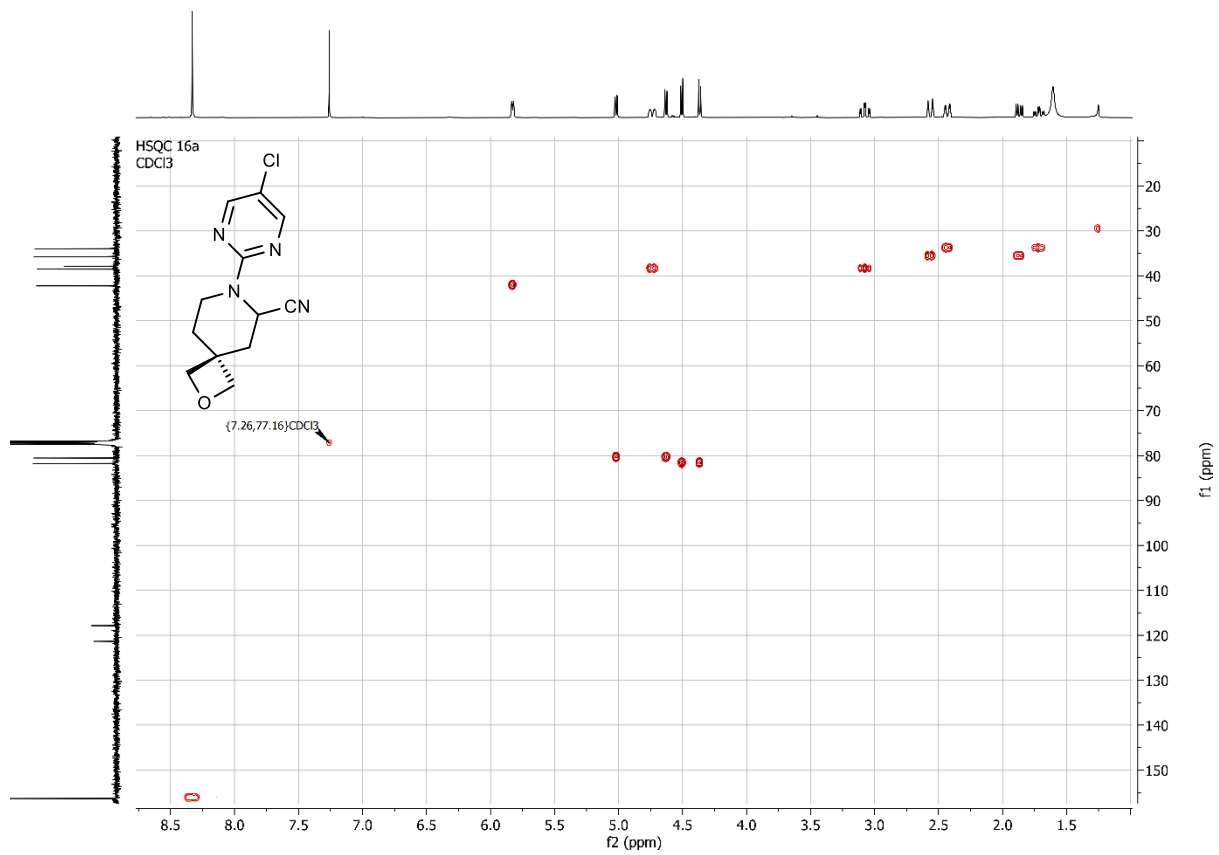


1H NMR 16a
400 MHz, CDCl3

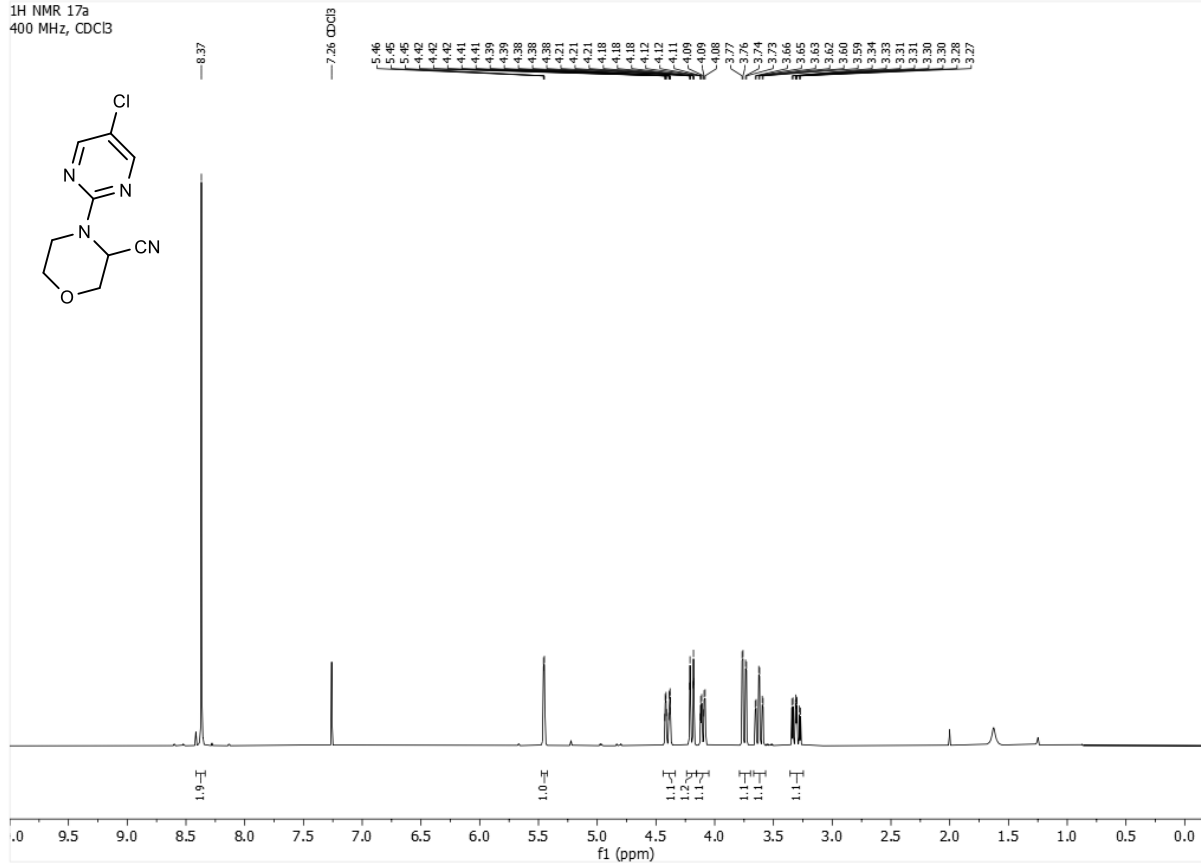


13C NMR 16a
101 MHz, CDCl3

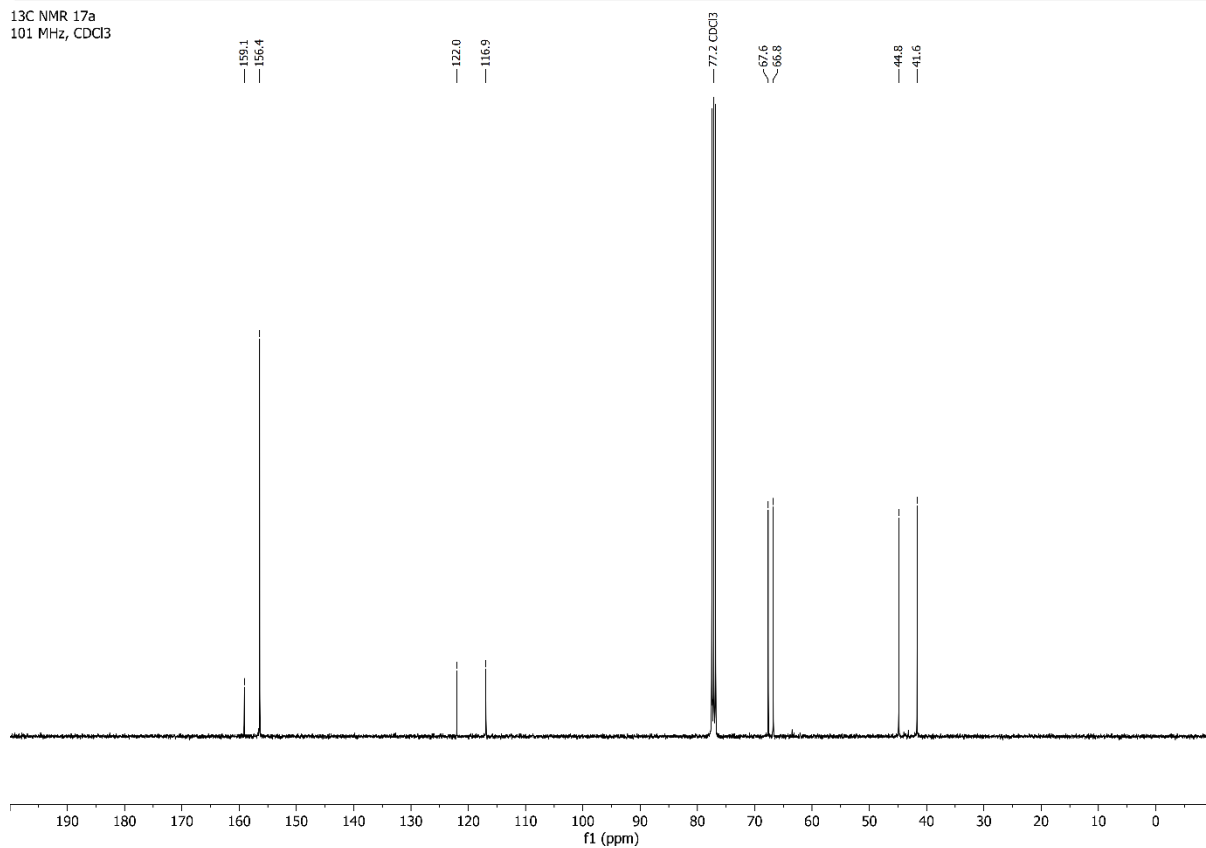


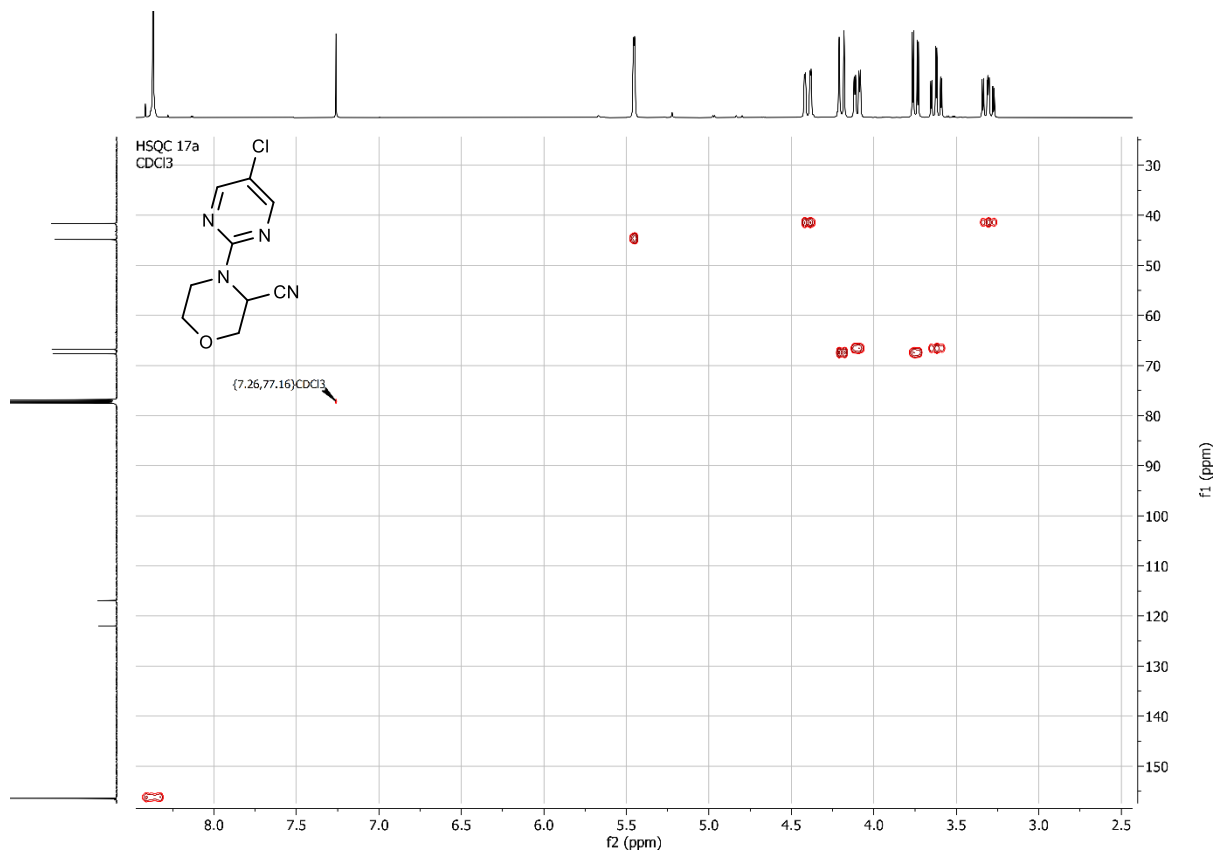


¹H NMR 17a
400 MHz, CDCl₃

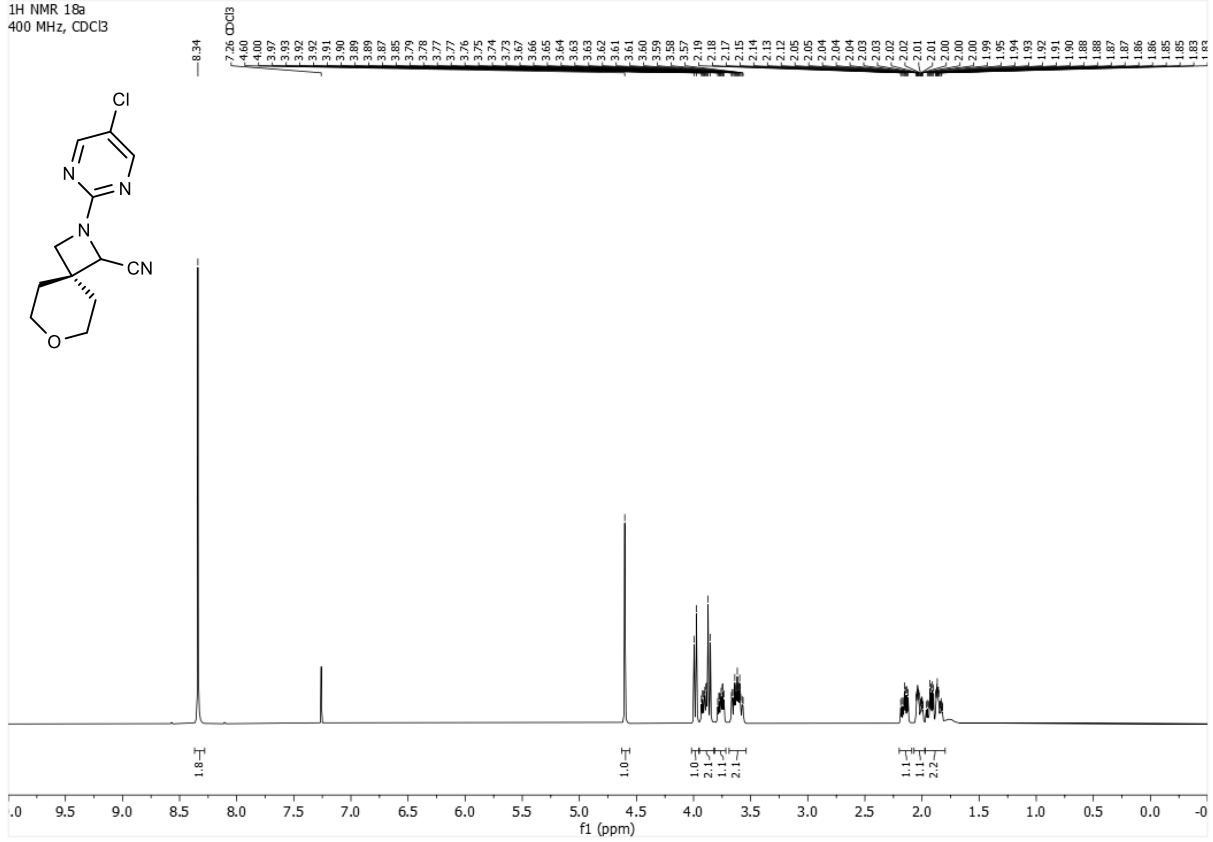


¹³C NMR 17a
101 MHz, CDCl₃

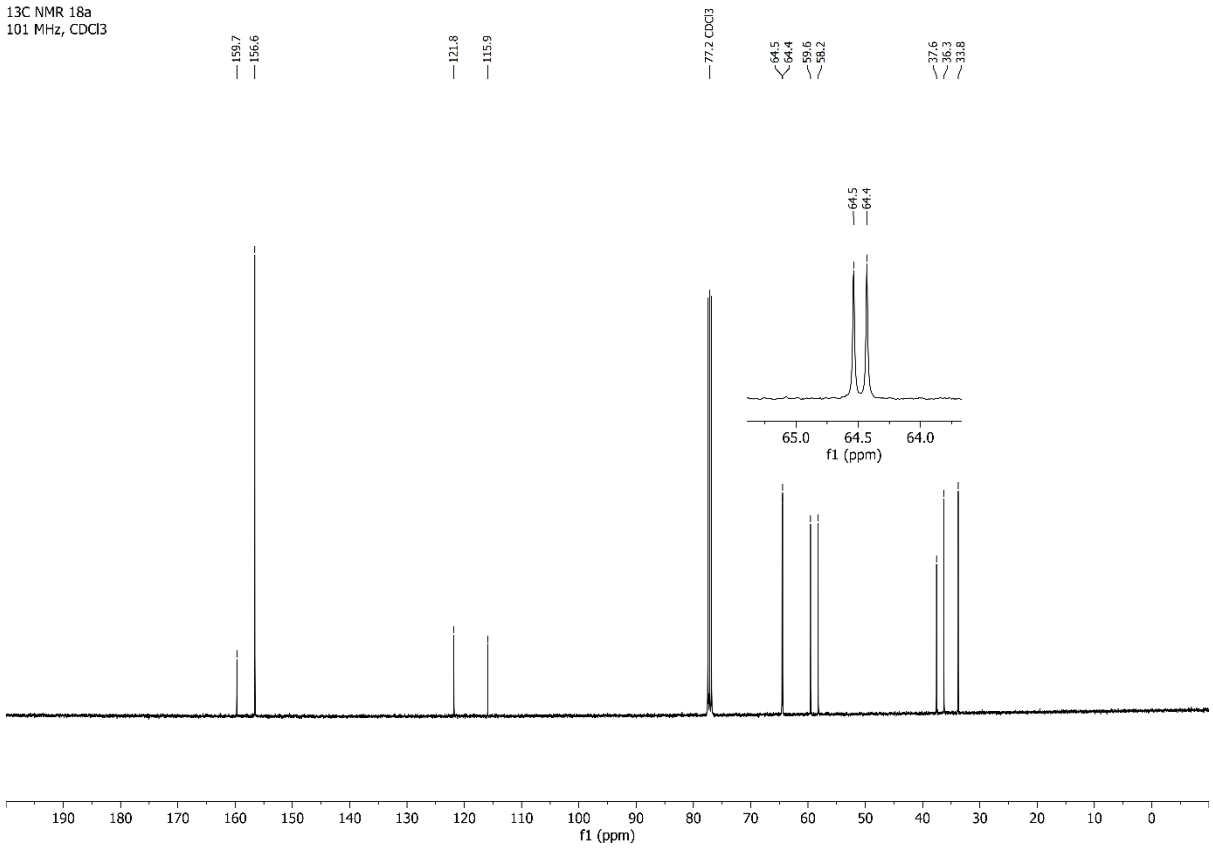


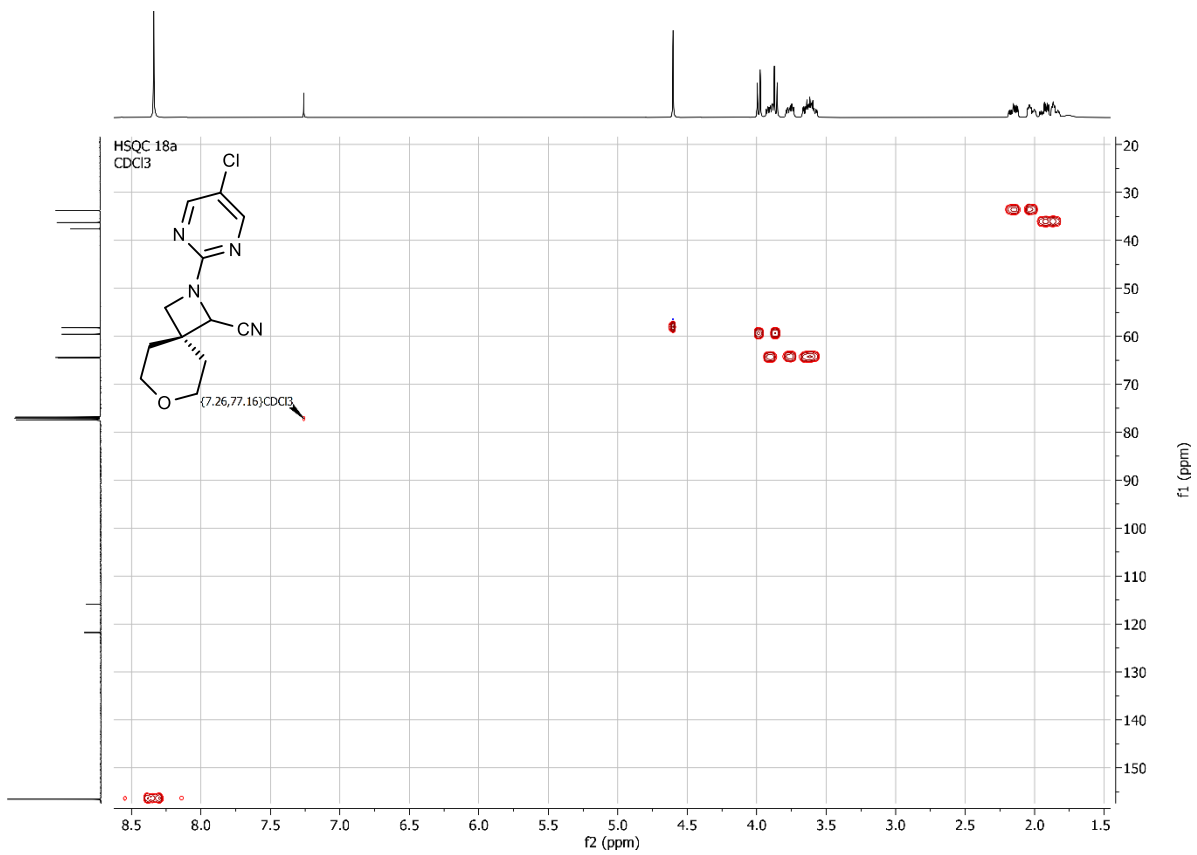


¹H NMR 18a
400 MHz, CDCl₃

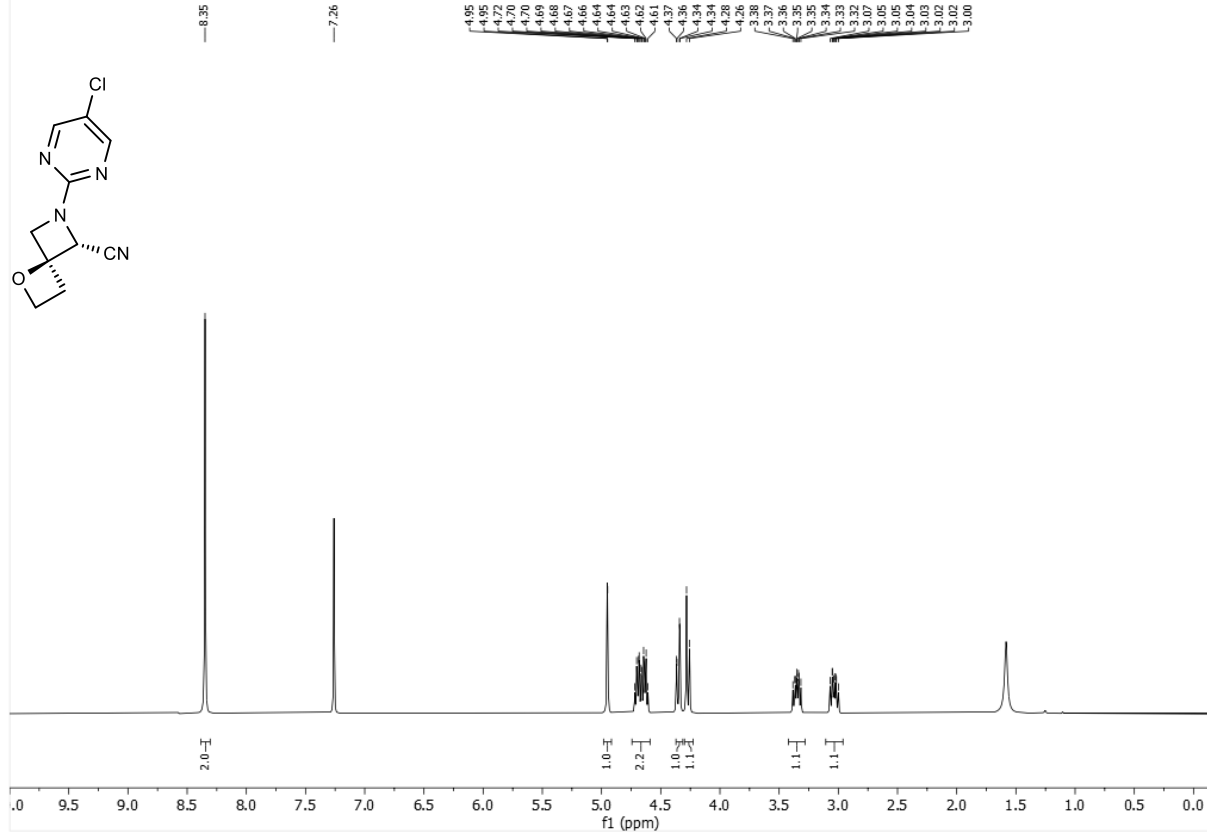


¹³C NMR 18a
101 MHz, CDCl₃

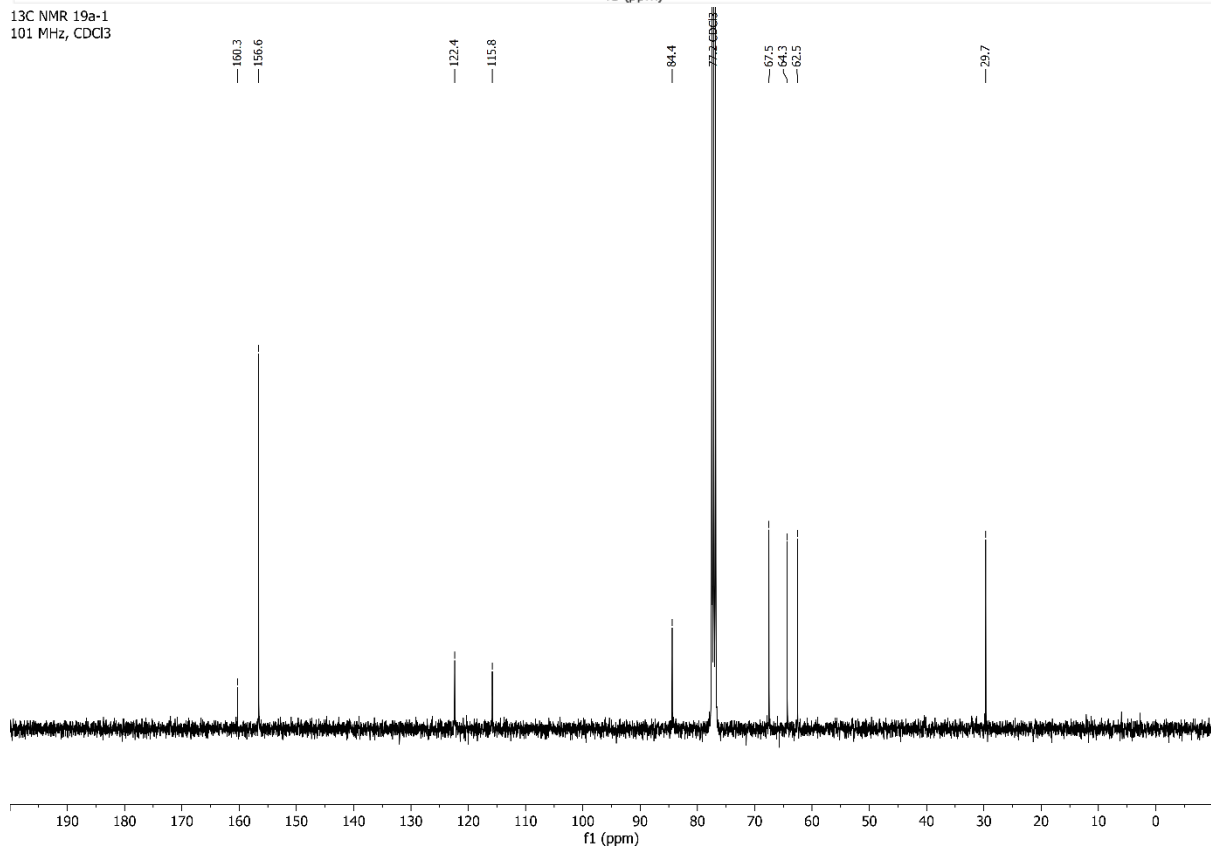


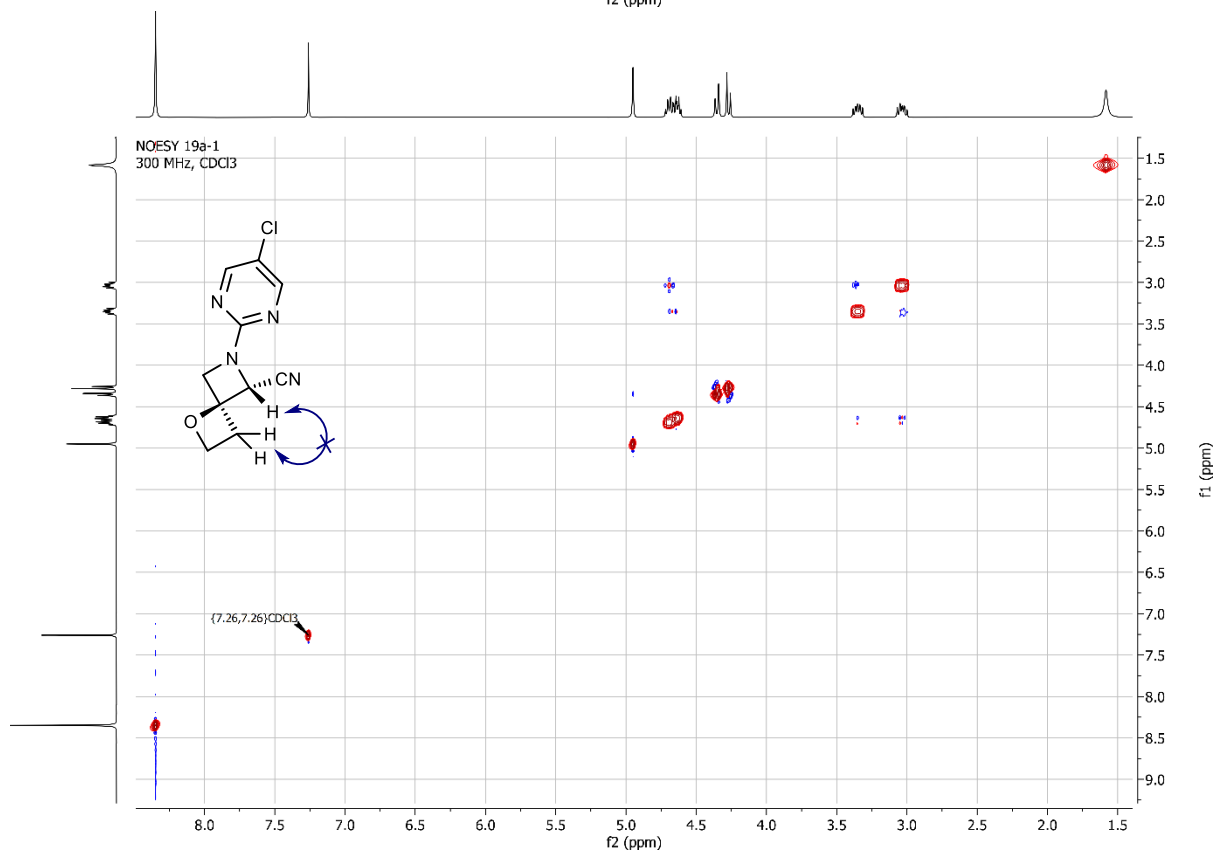
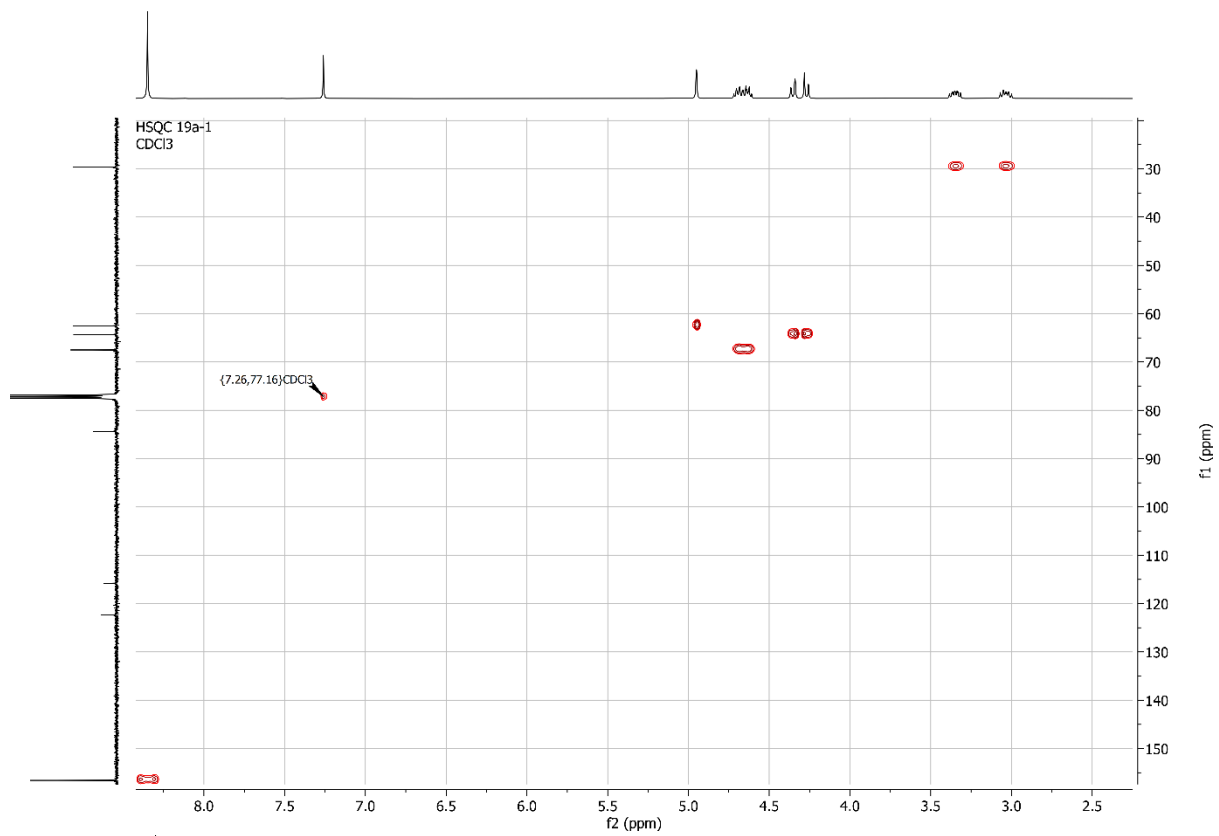


¹H NMR 19a-1
400 MHz, CDCl₃

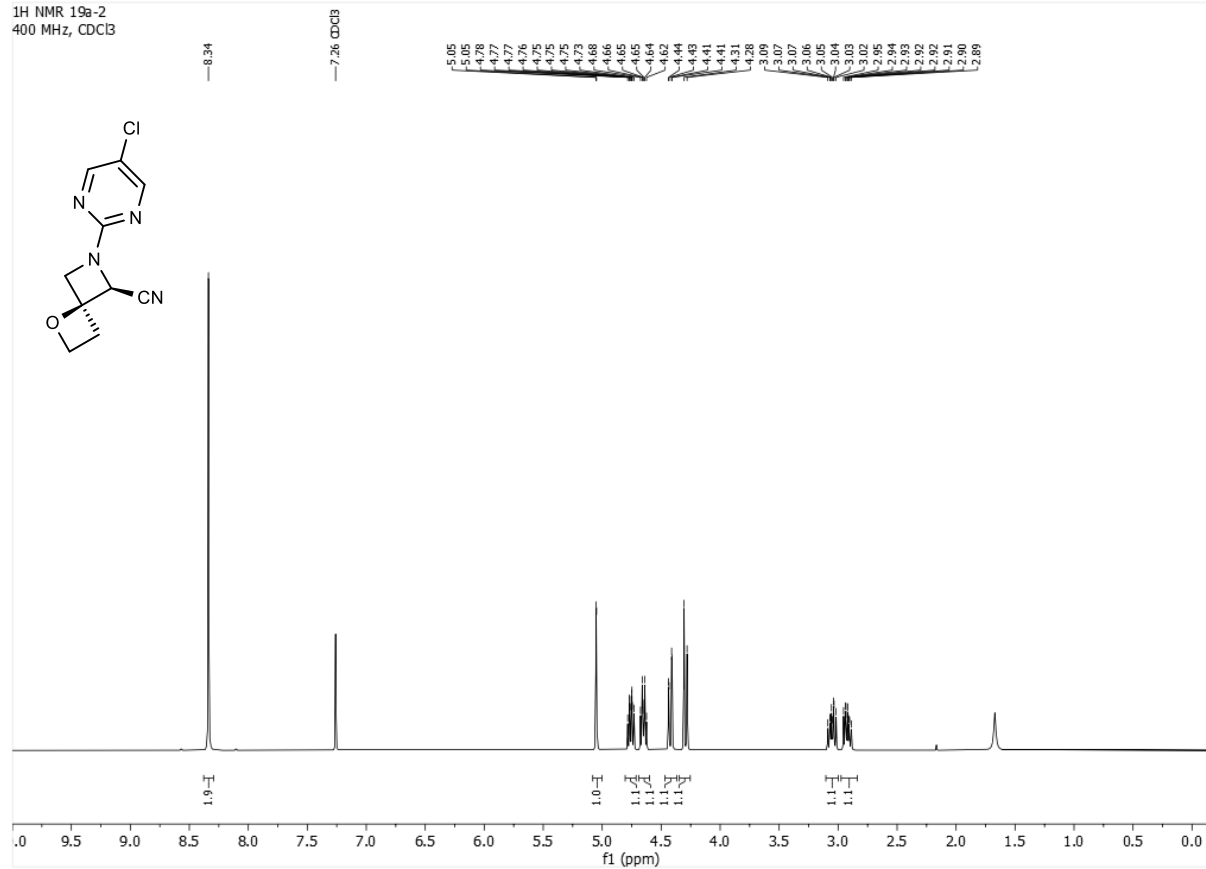


¹³C NMR 19a-1
101 MHz, CDCl₃

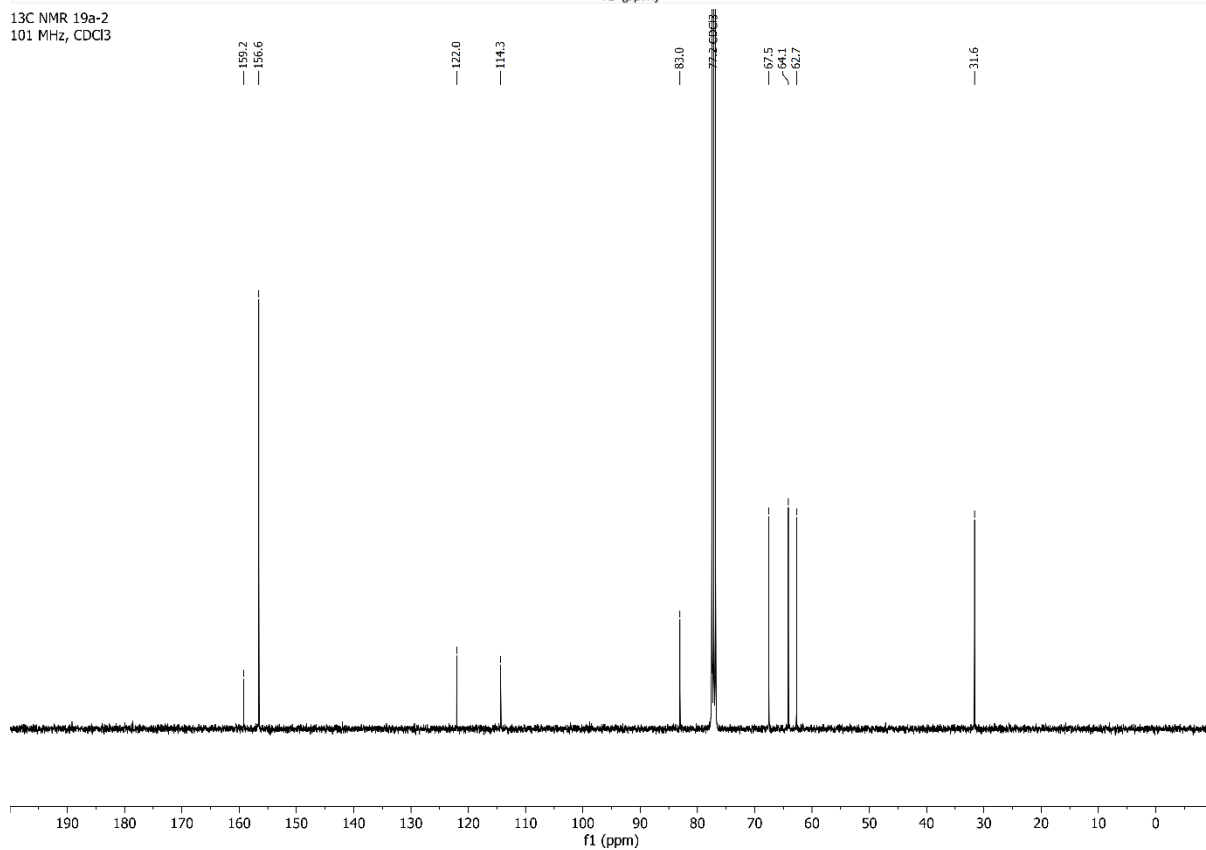


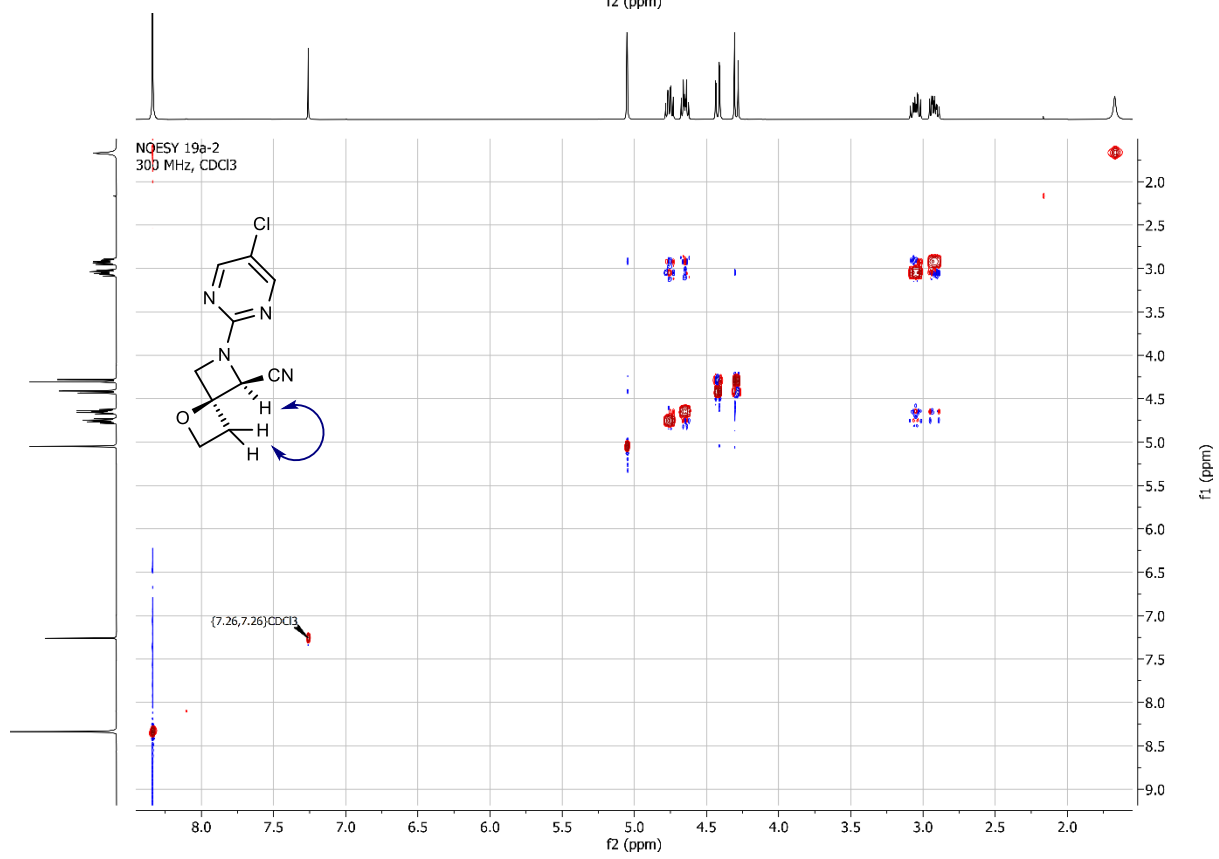
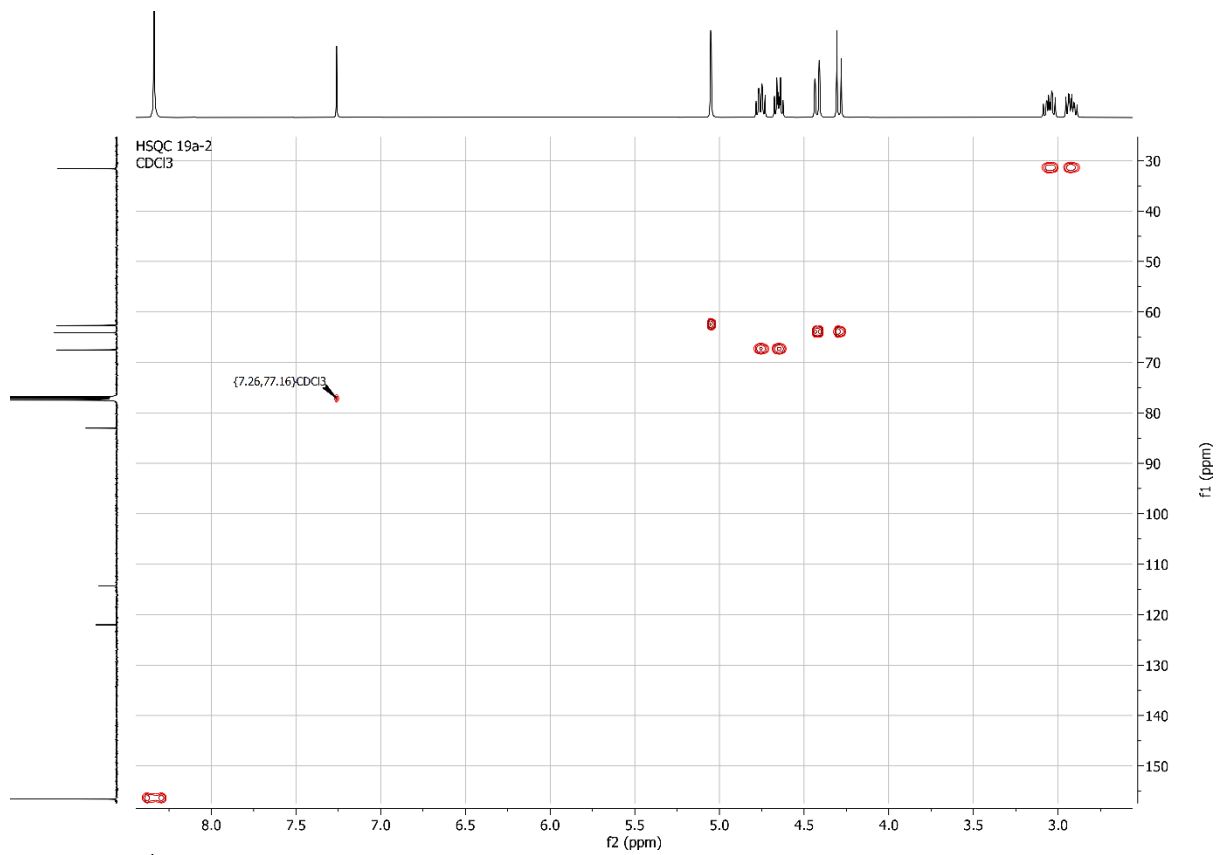


¹H NMR 19a-2
400 MHz, CDCl₃

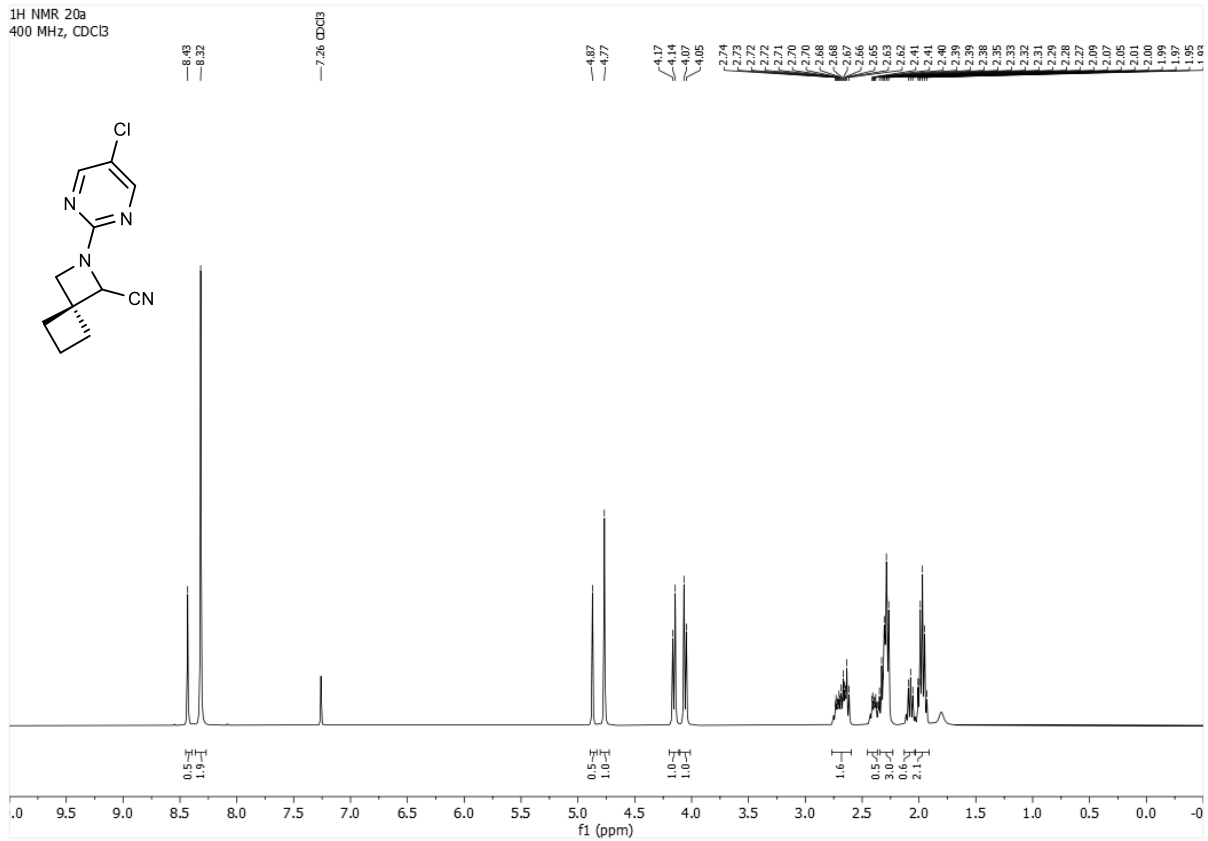


¹³C NMR 19a-2
101 MHz, CDCl₃

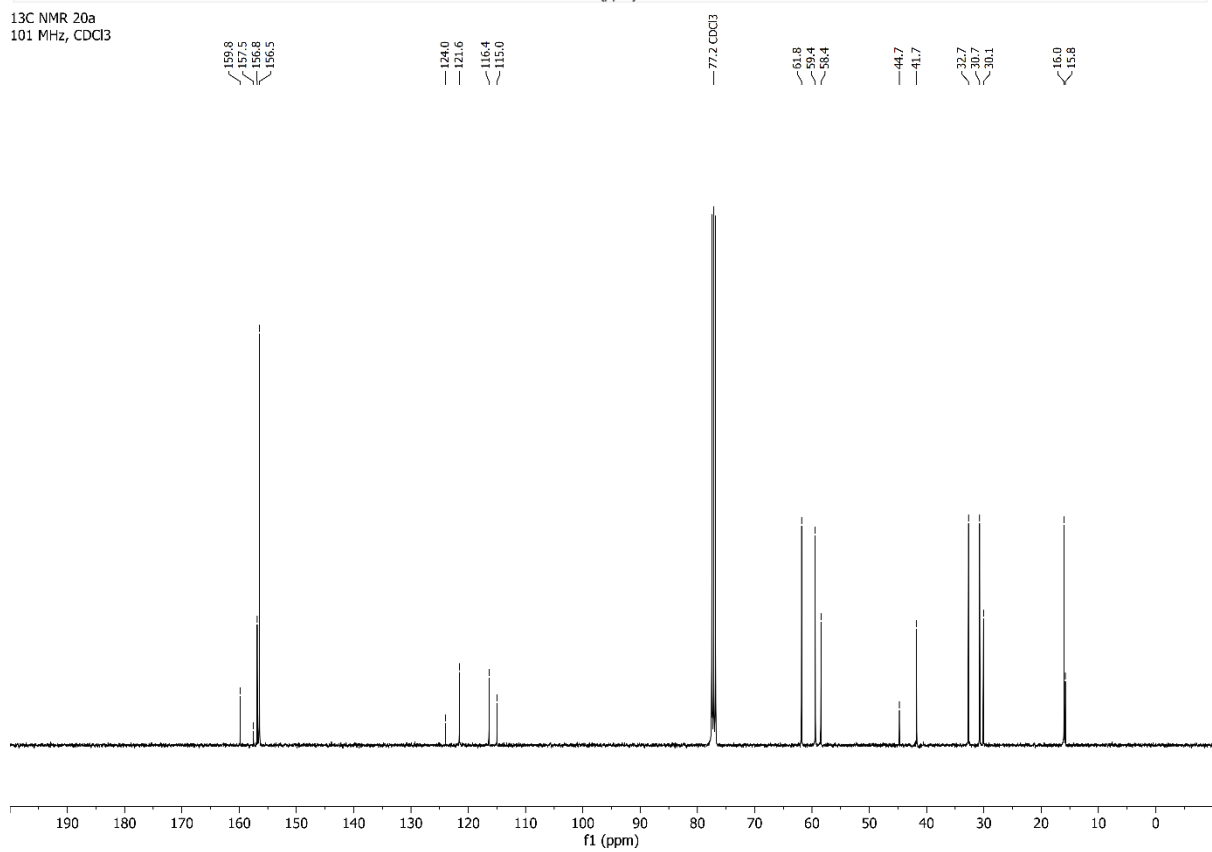


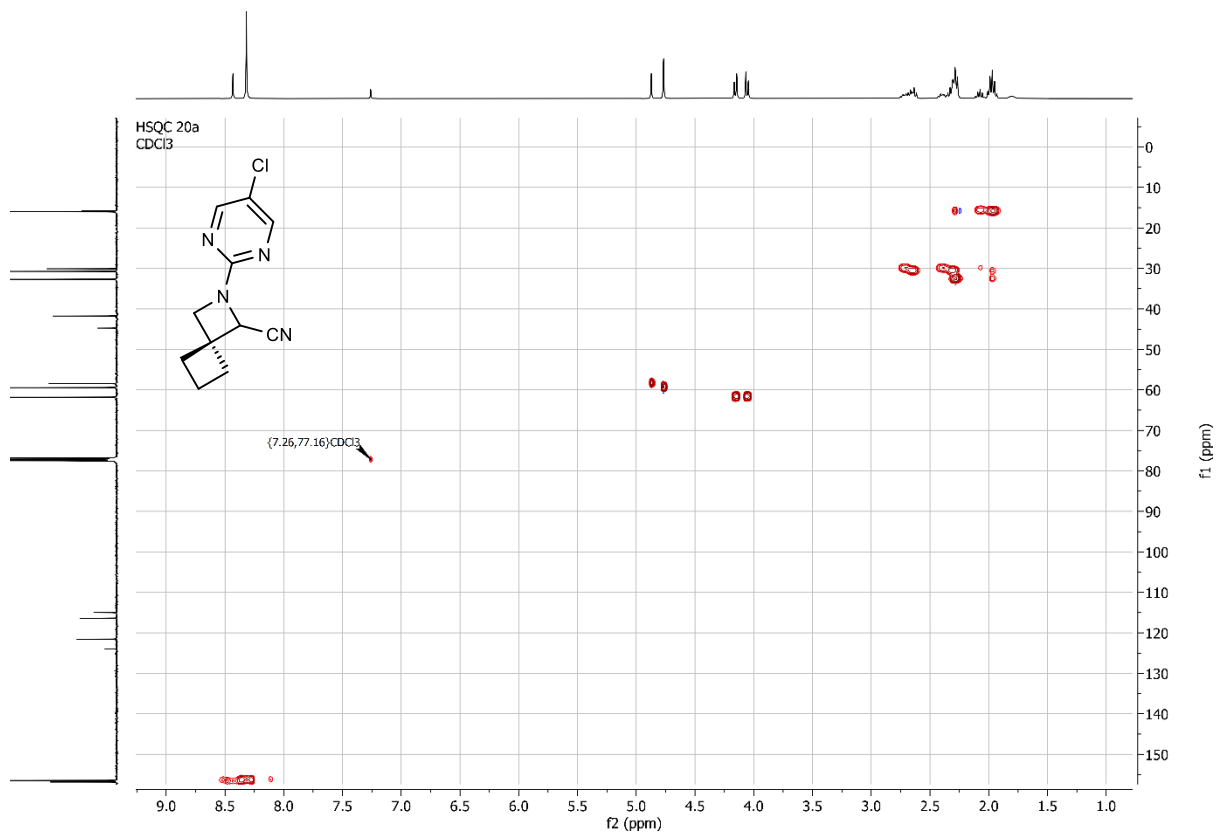


¹H NMR 20a
400 MHz, CDCl₃

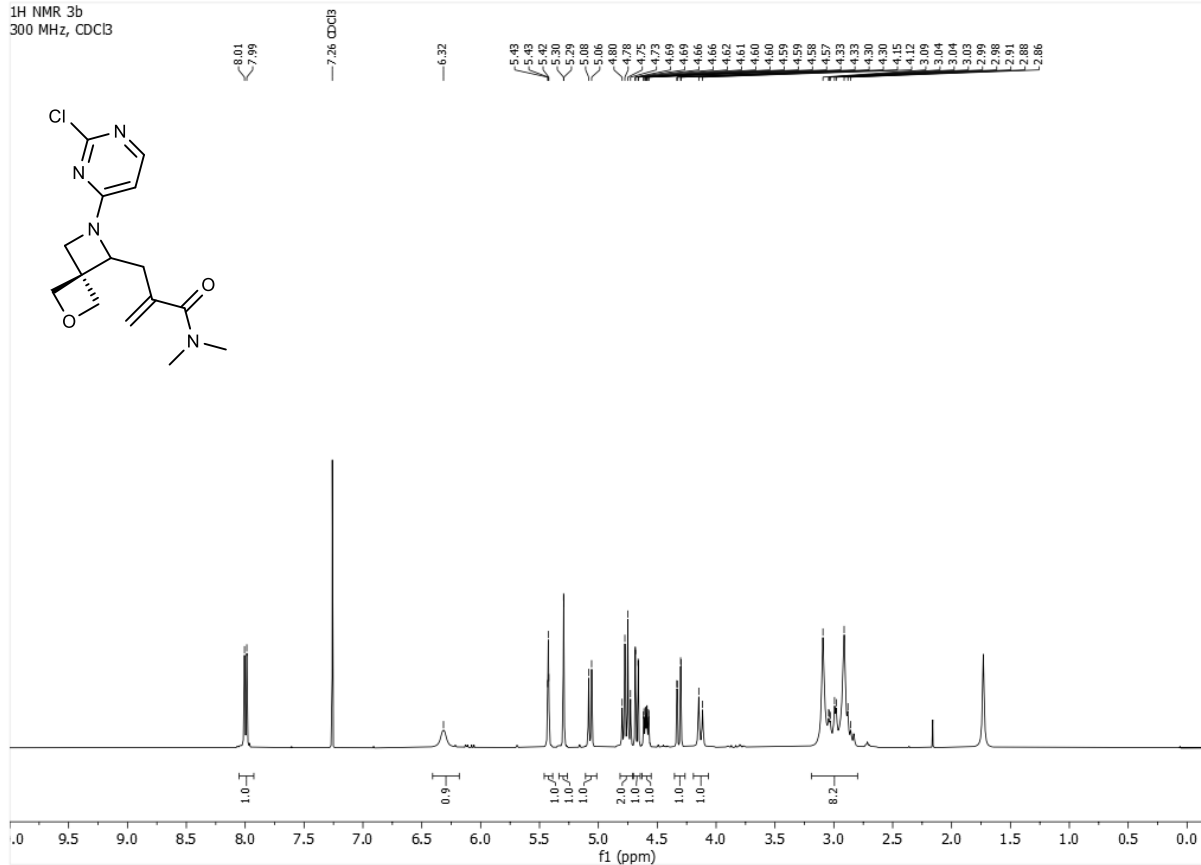


¹³C NMR 20a
101 MHz, CDCl₃

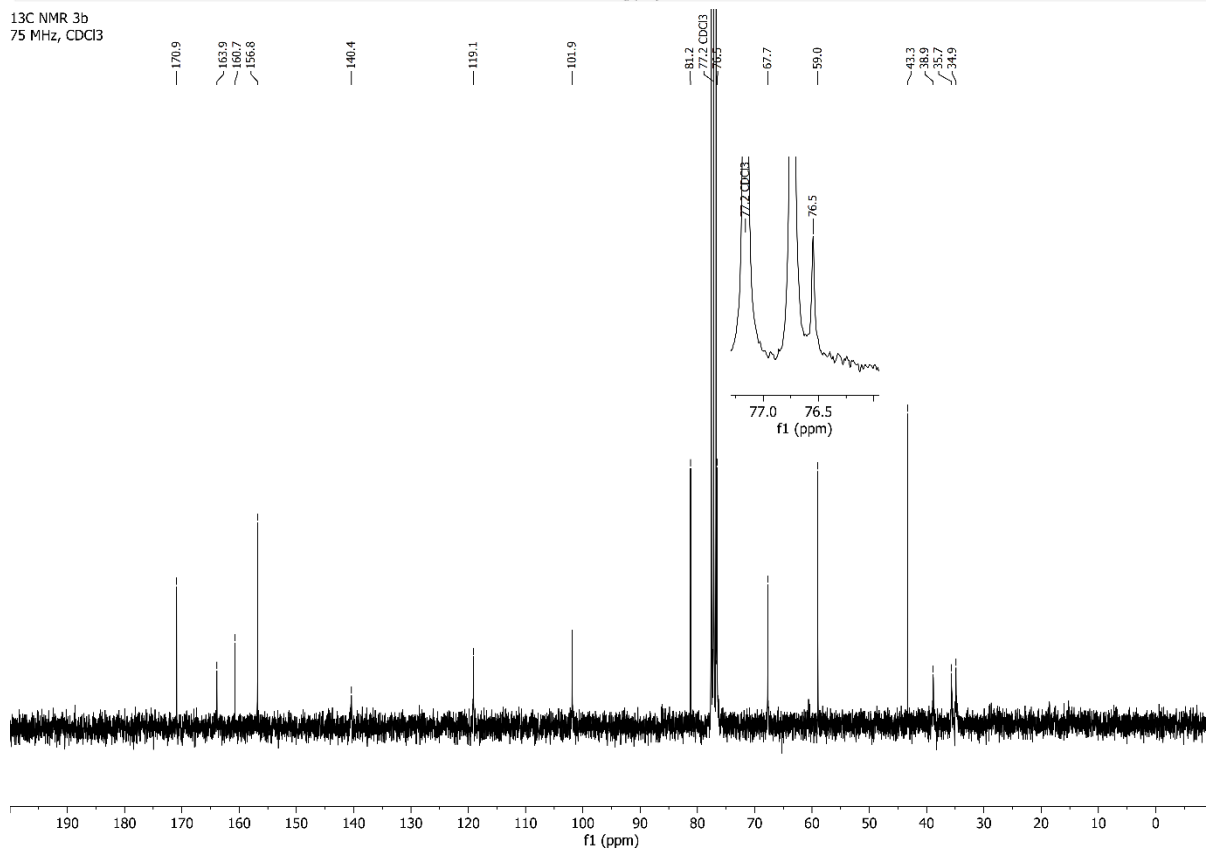




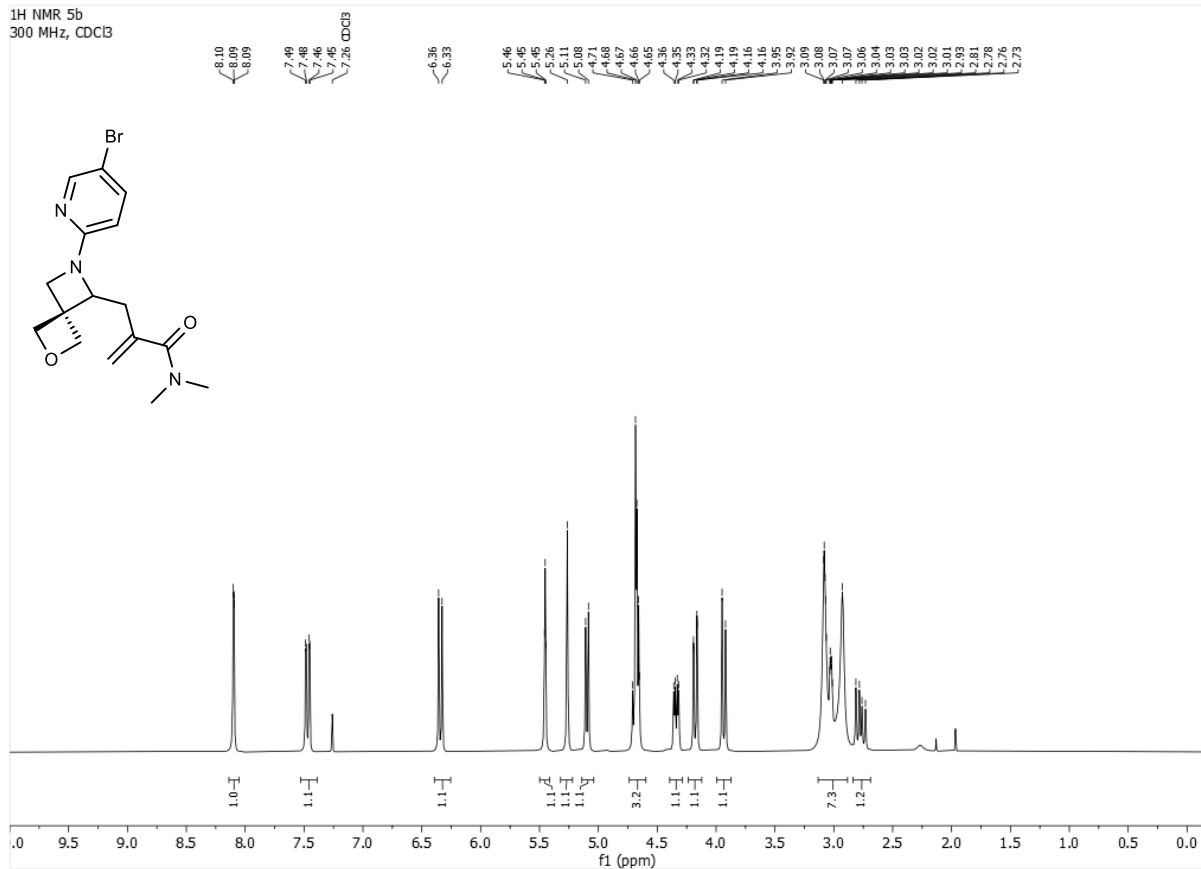
1H NMR 3b
300 MHz, CDCl3



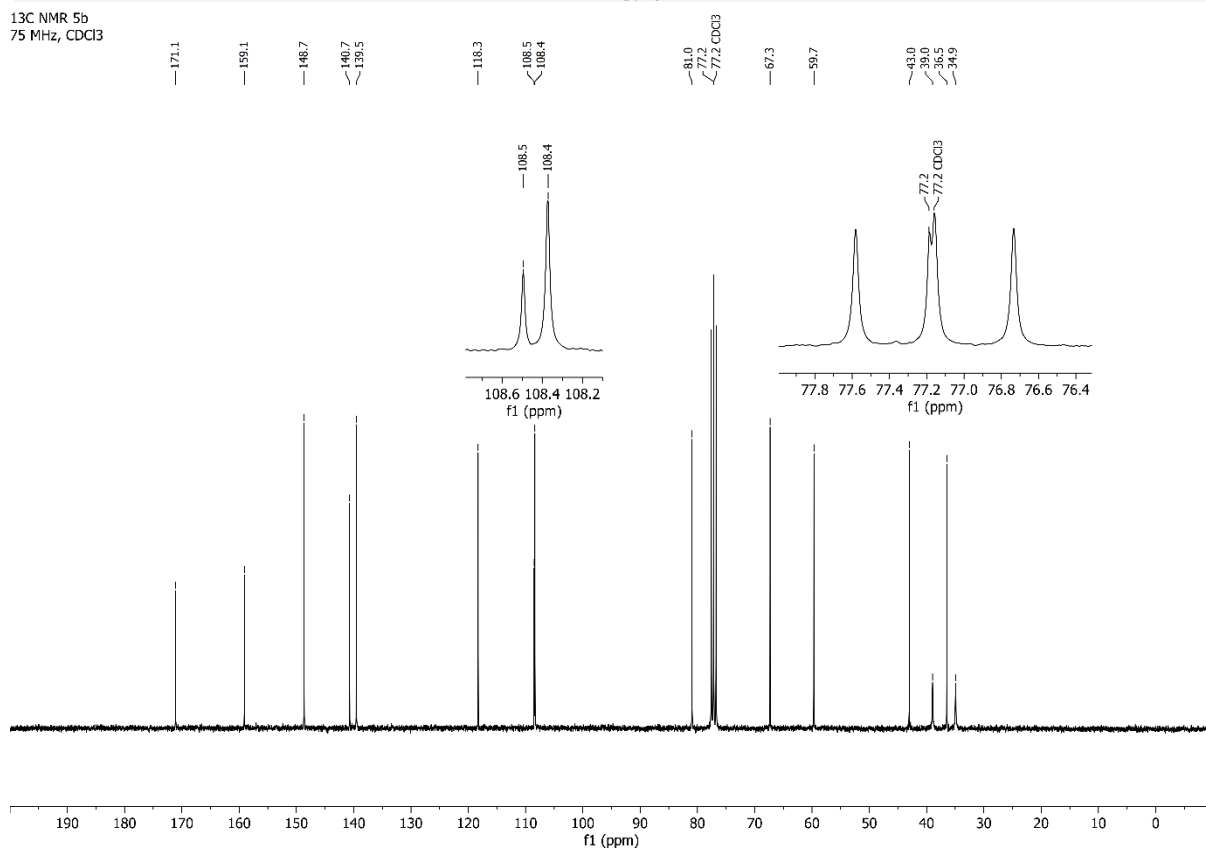
13C NMR 3b
75 MHz, CDCl3



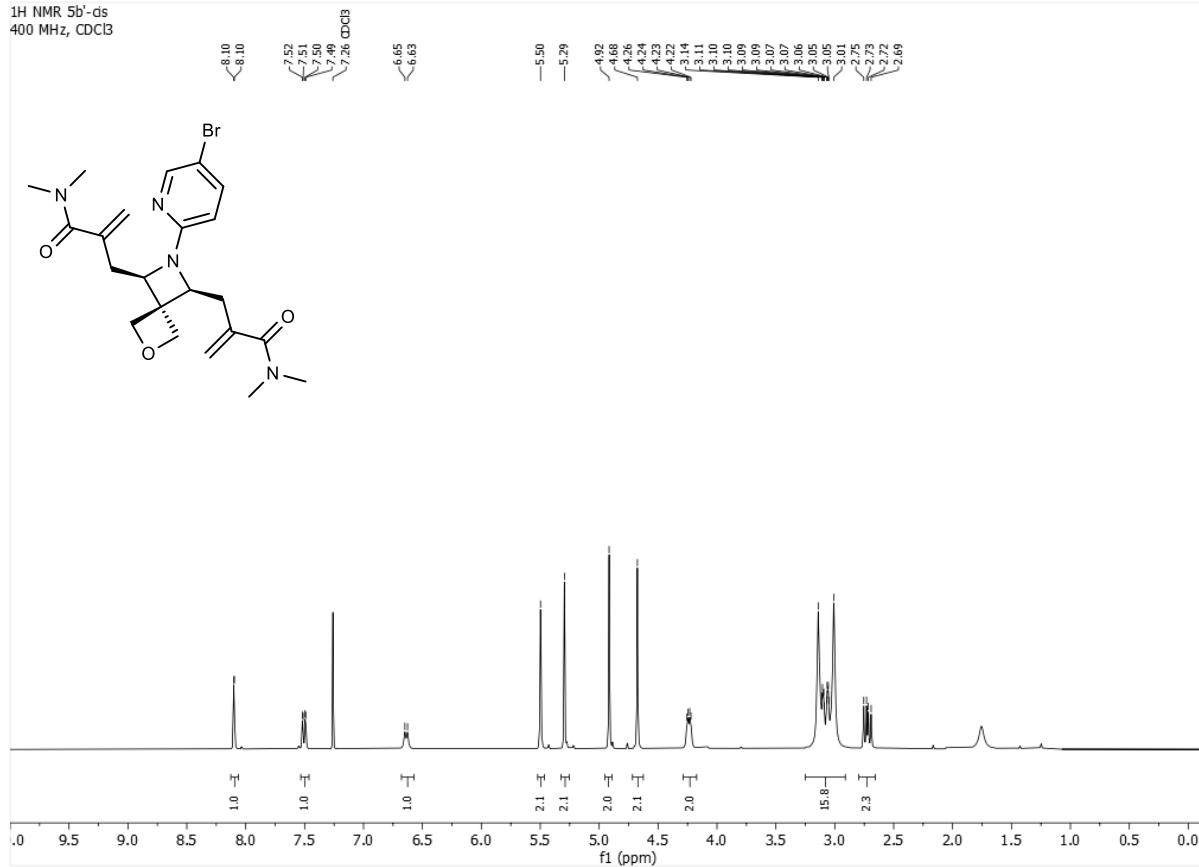
¹H NMR 5b
300 MHz, CDCl₃



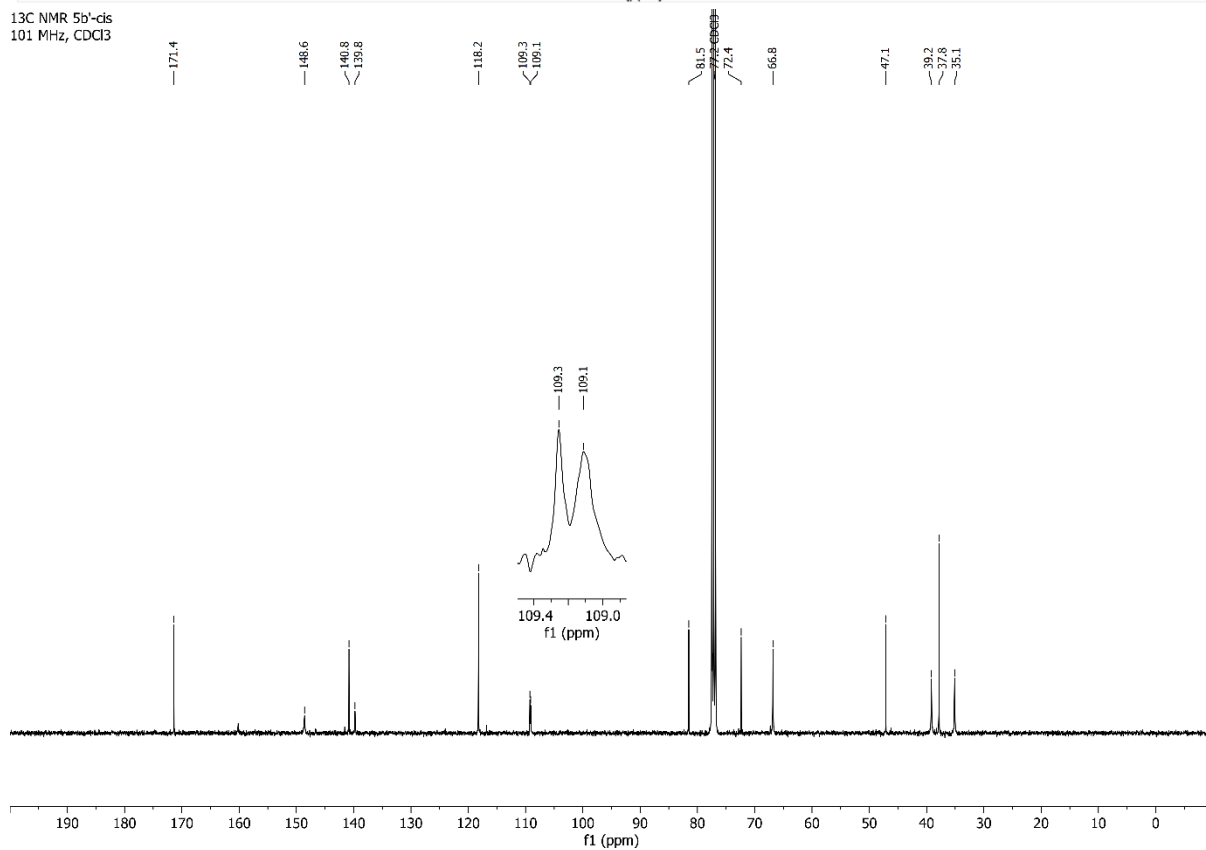
¹³C NMR 5b
75 MHz, CDCl₃



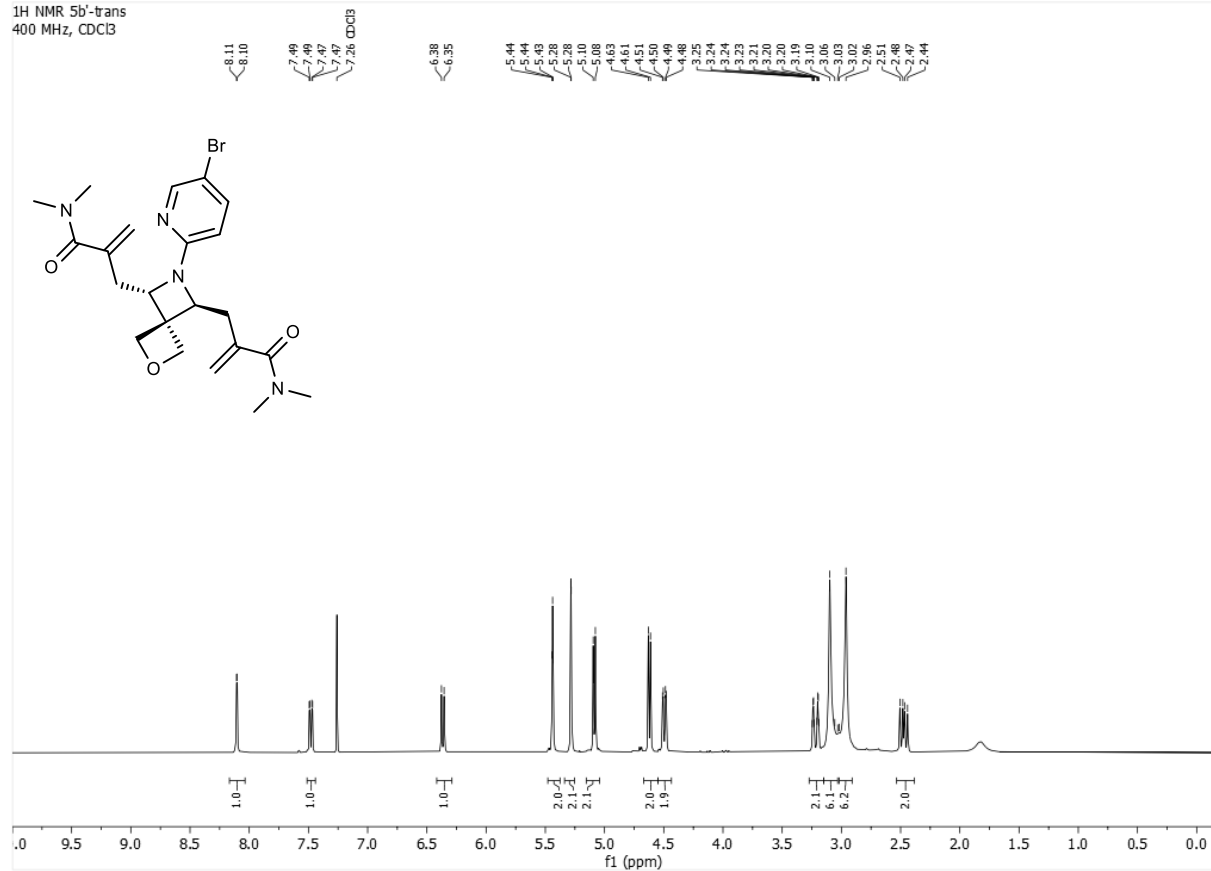
¹H NMR 5b'-cis
400 MHz, CDCl₃



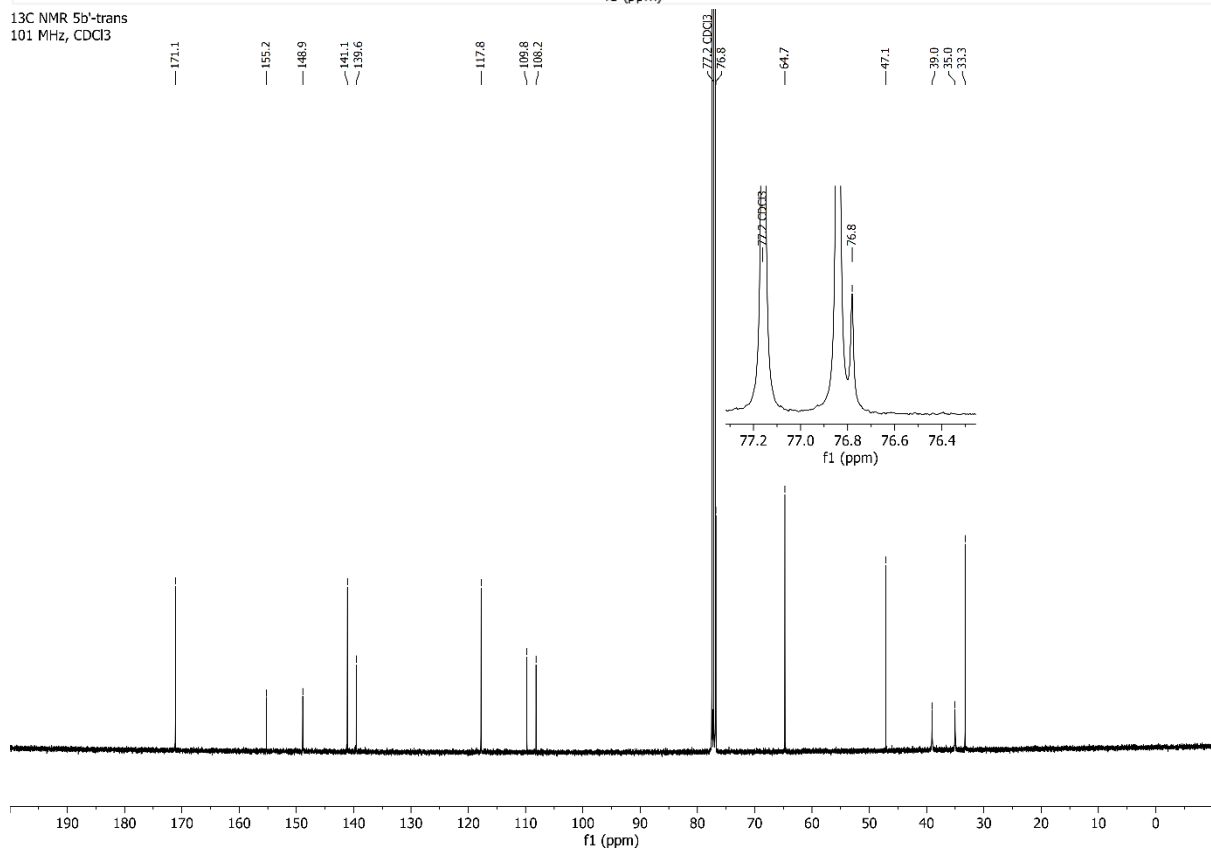
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101 MHz, CDCl₃



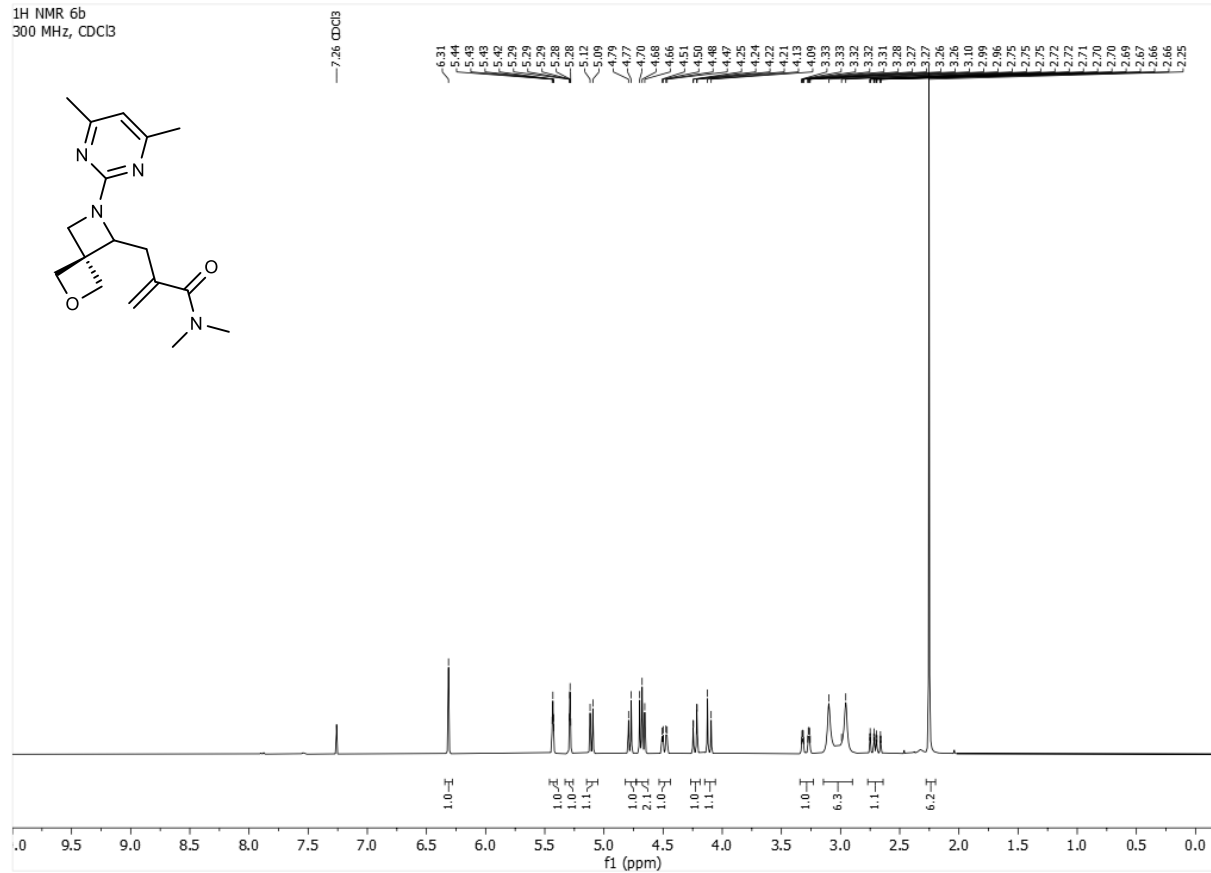
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400 MHz, CDCl₃



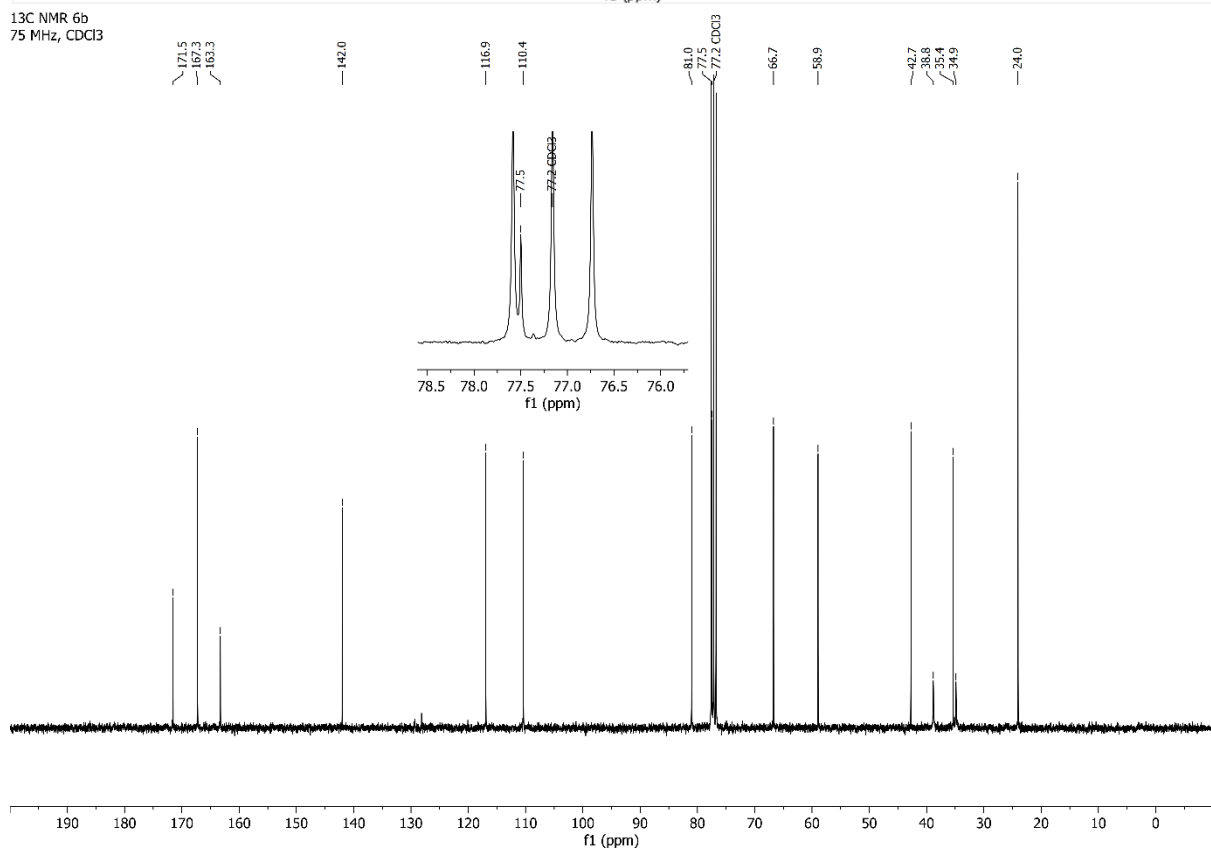
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101 MHz, CDCl₃



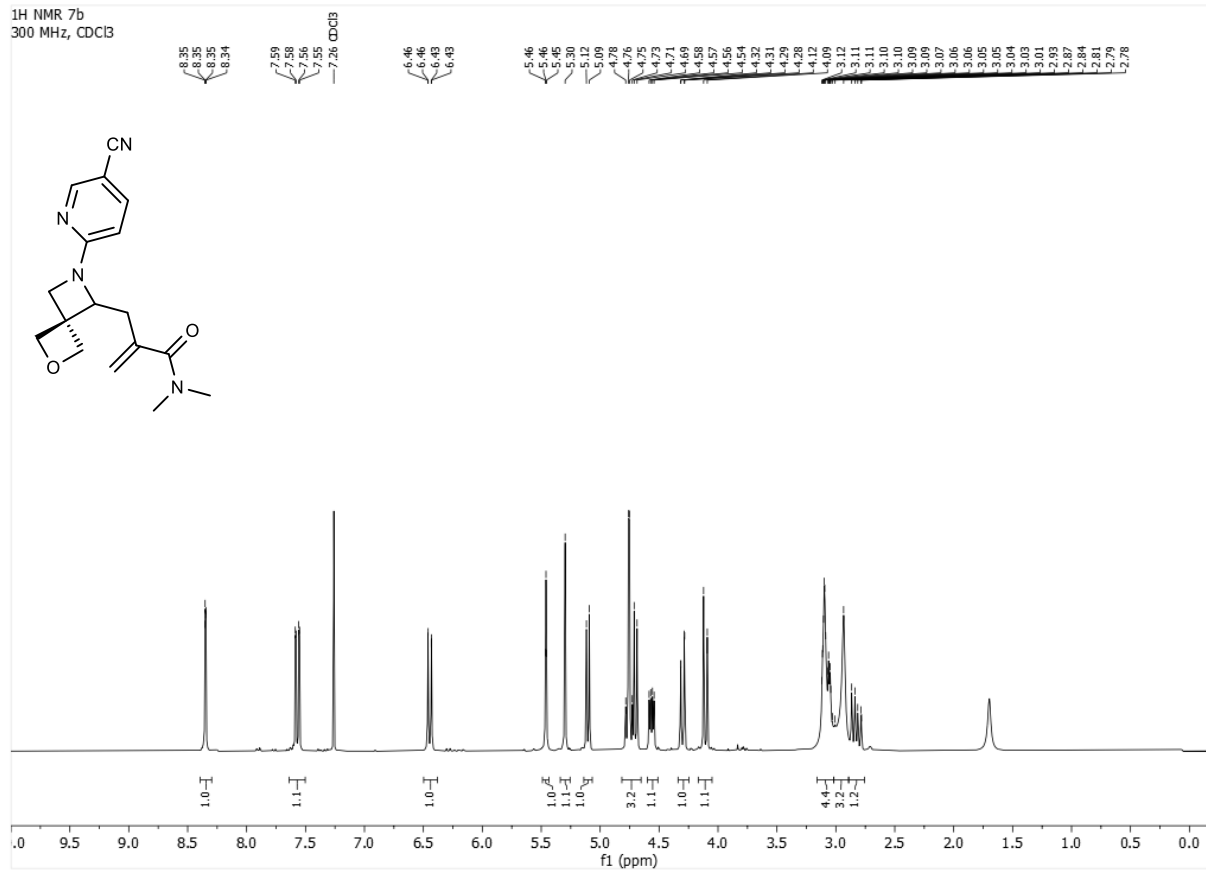
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300 MHz, CDCl₃



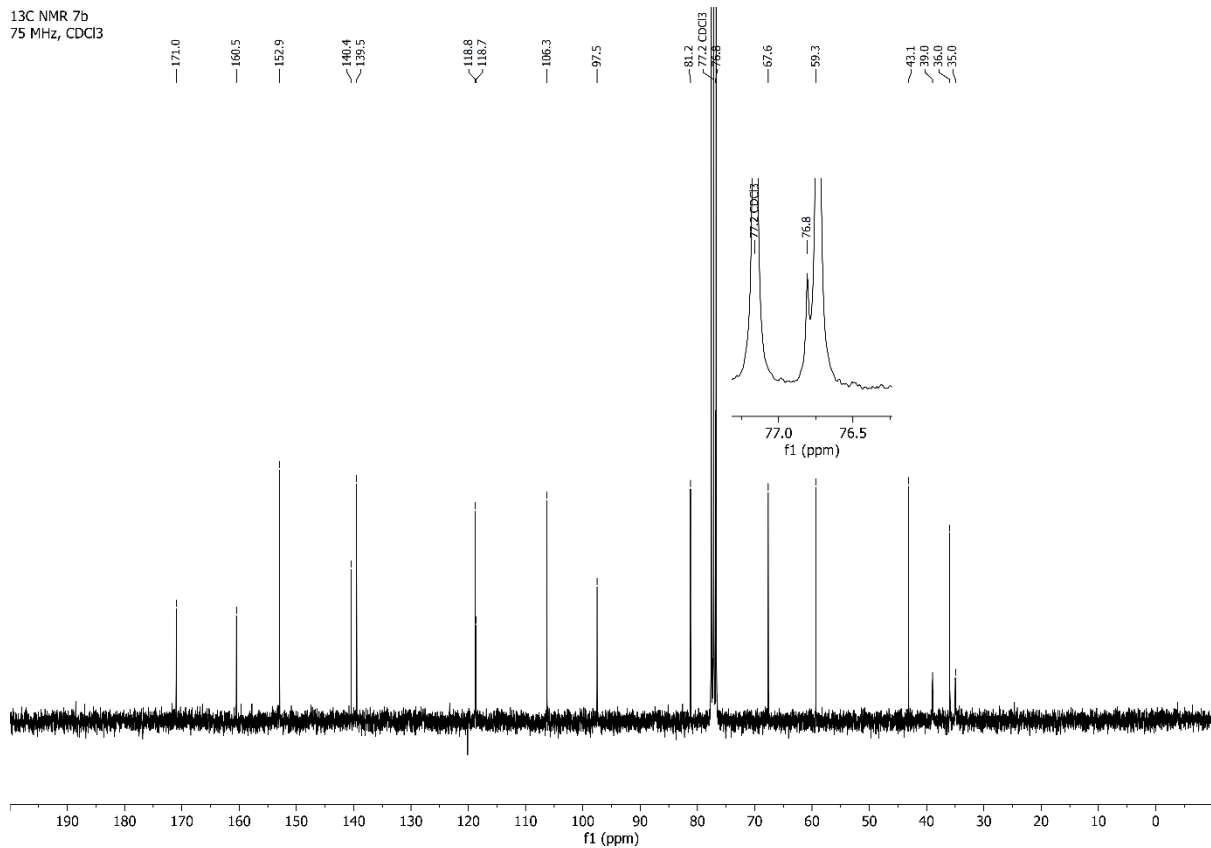
¹³C NMR 6b
75 MHz, CDCl₃



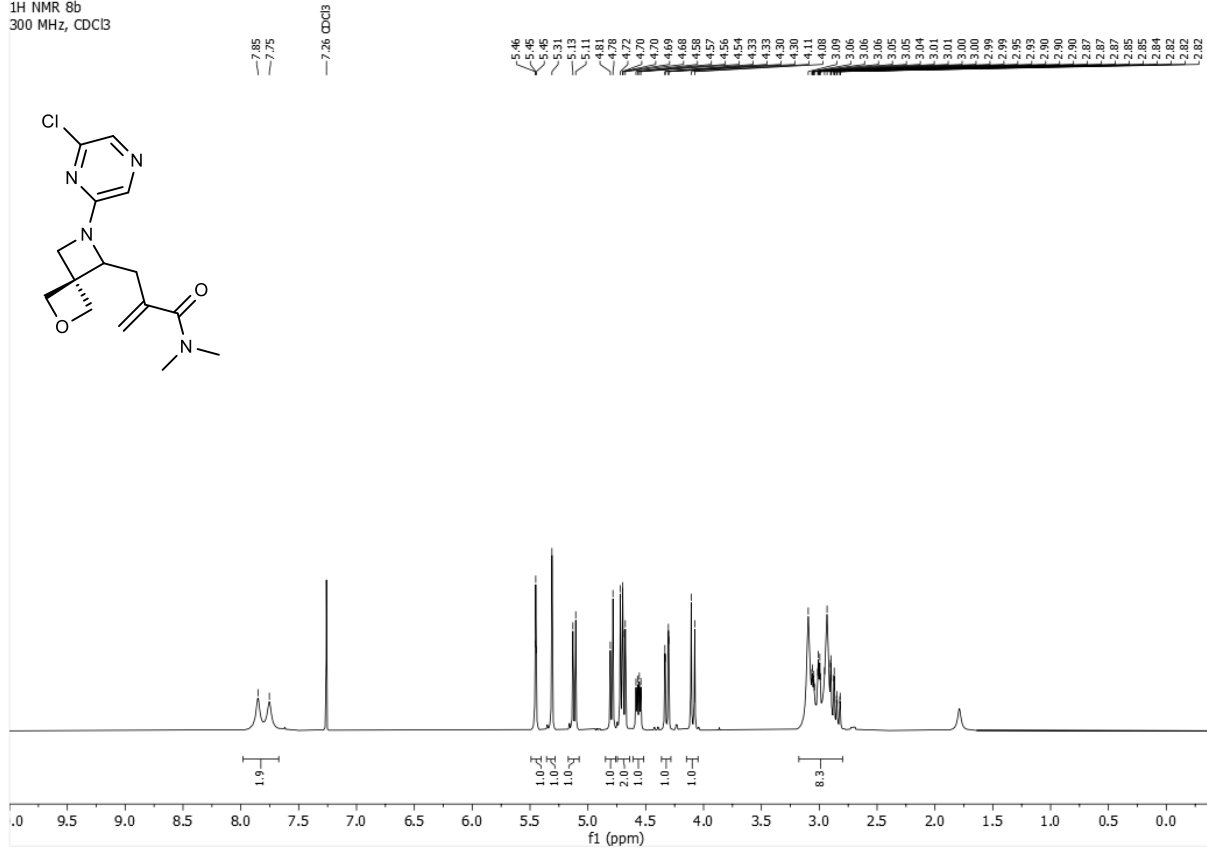
1H NMR 7b
300 MHz, CDCl₃



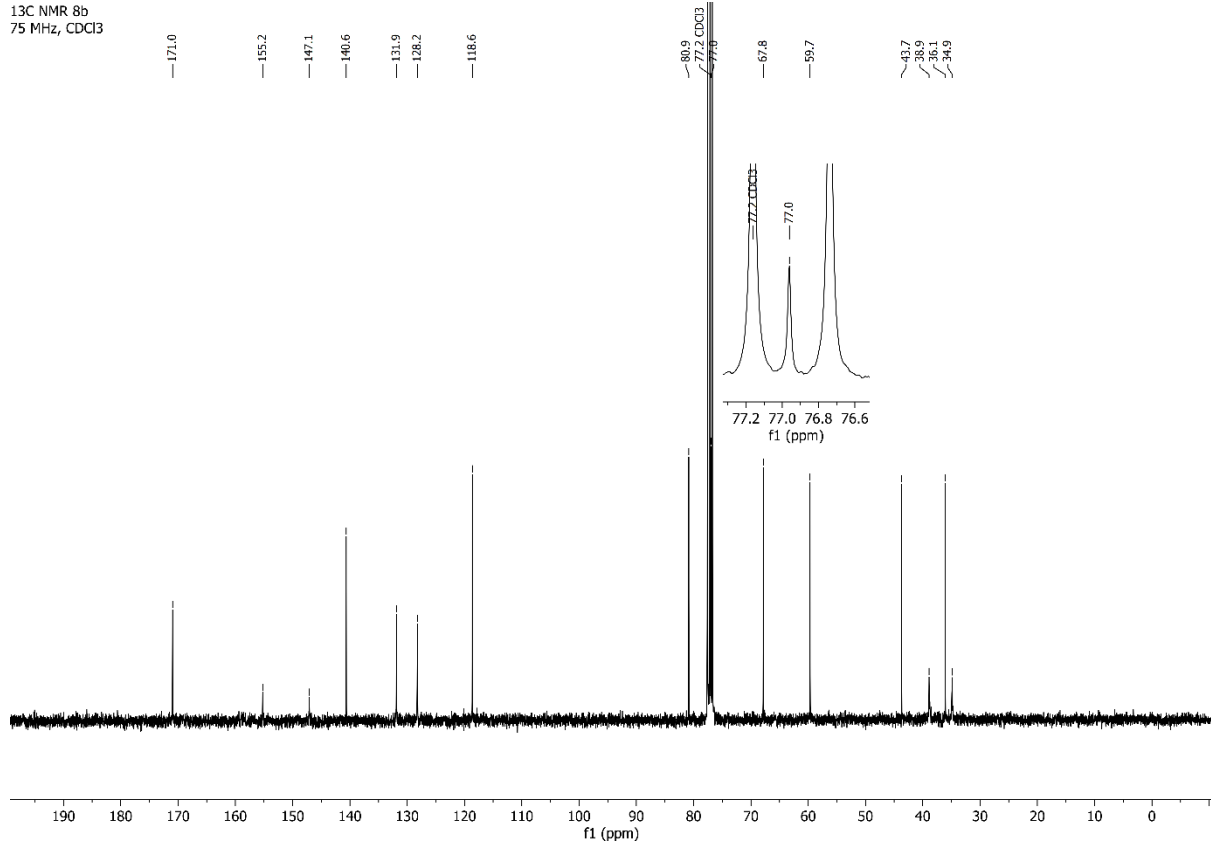
13C NMR 7b
75 MHz, CDCl₃



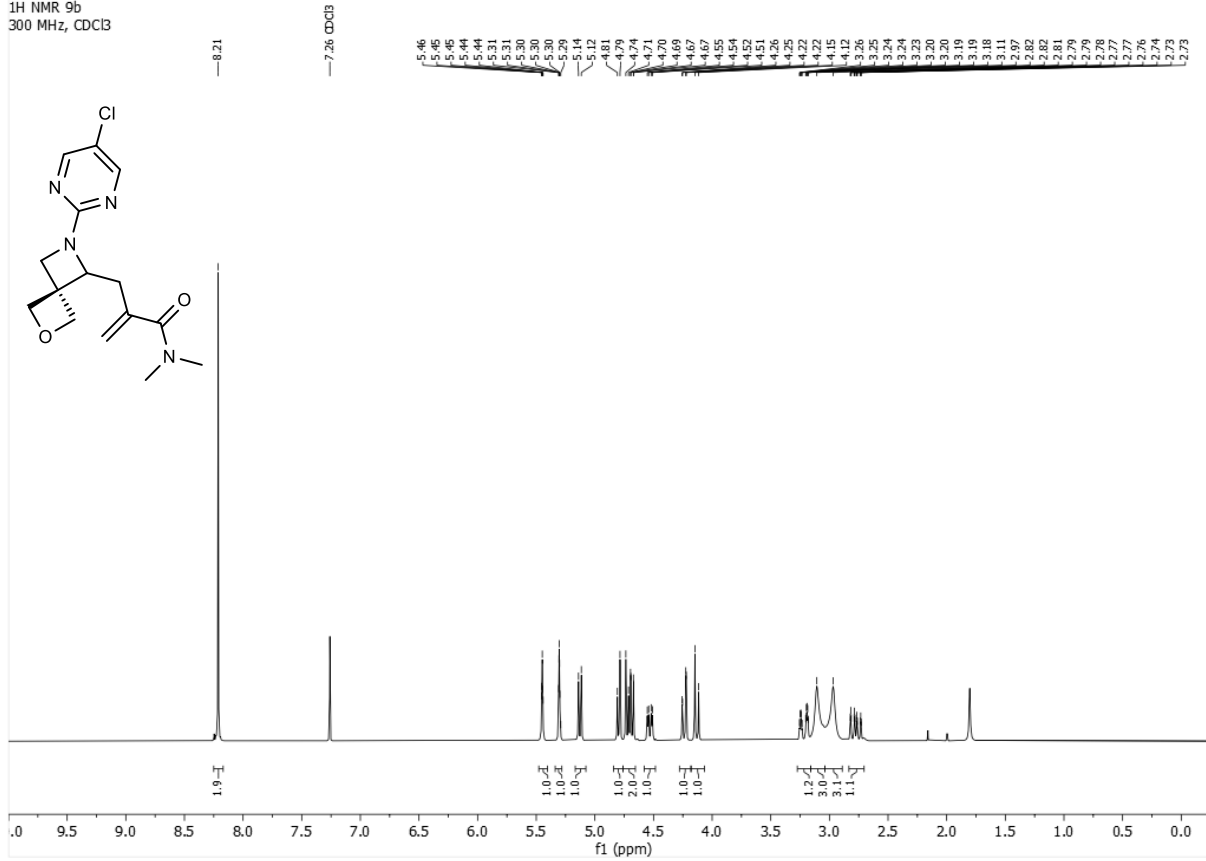
¹H NMR 8b
300 MHz, CDCl₃



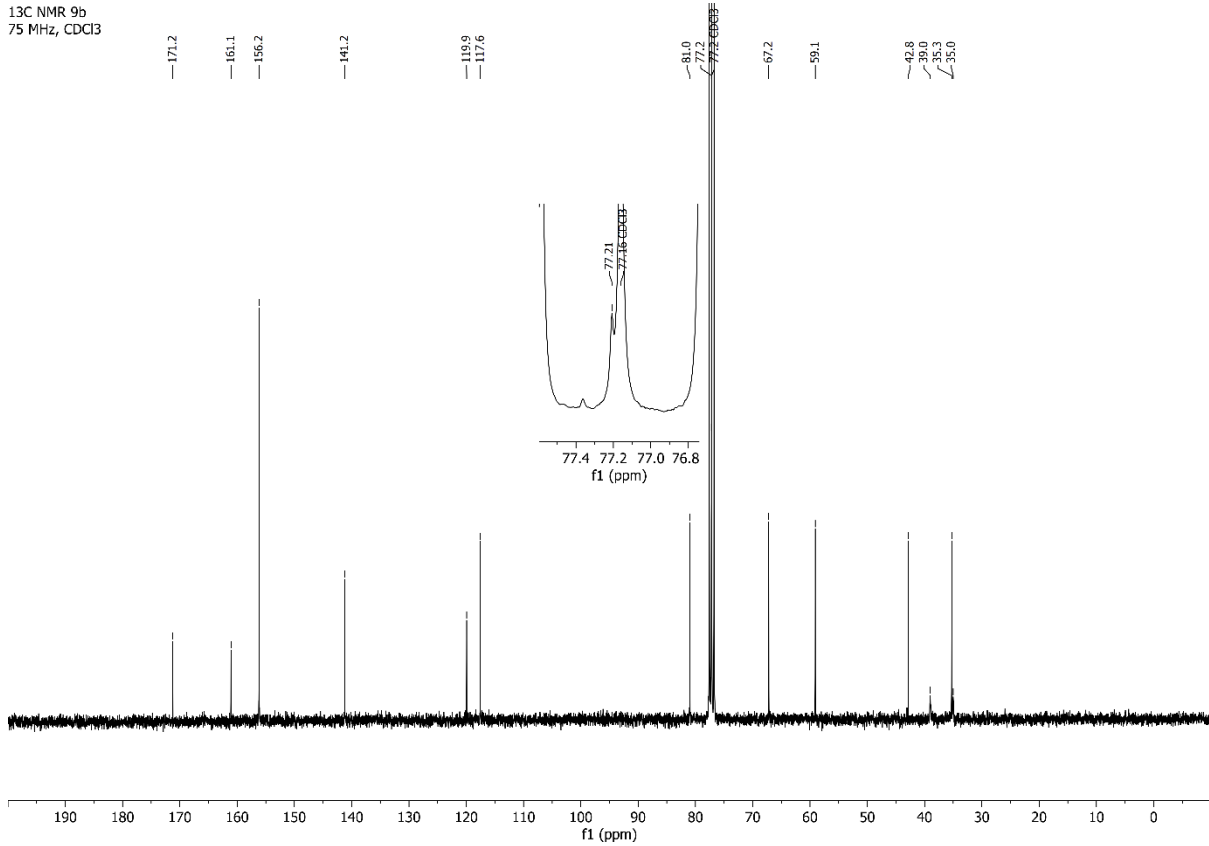
¹³C NMR 8b
75 MHz, CDCl₃



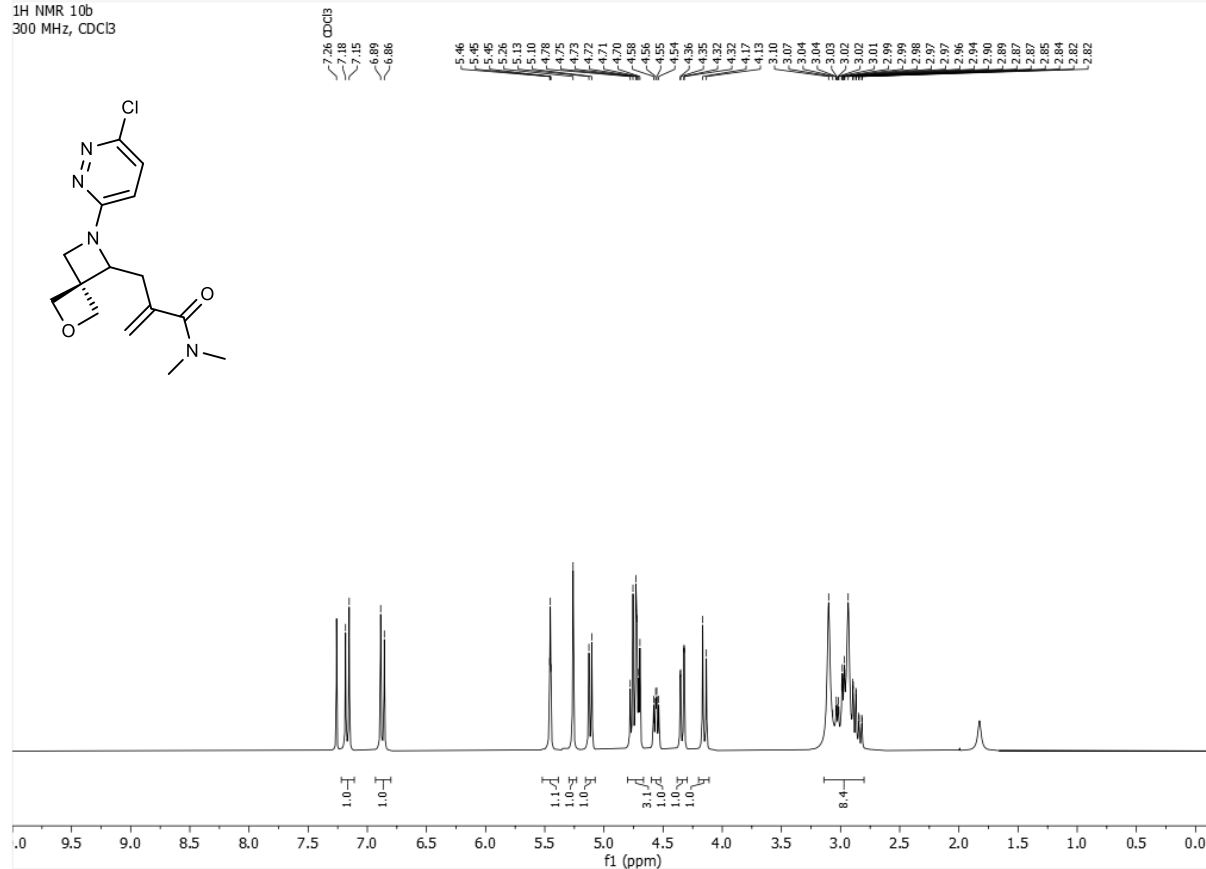
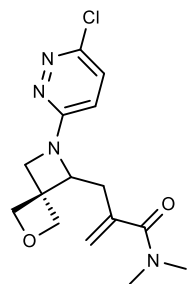
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300 MHz, CDCl₃



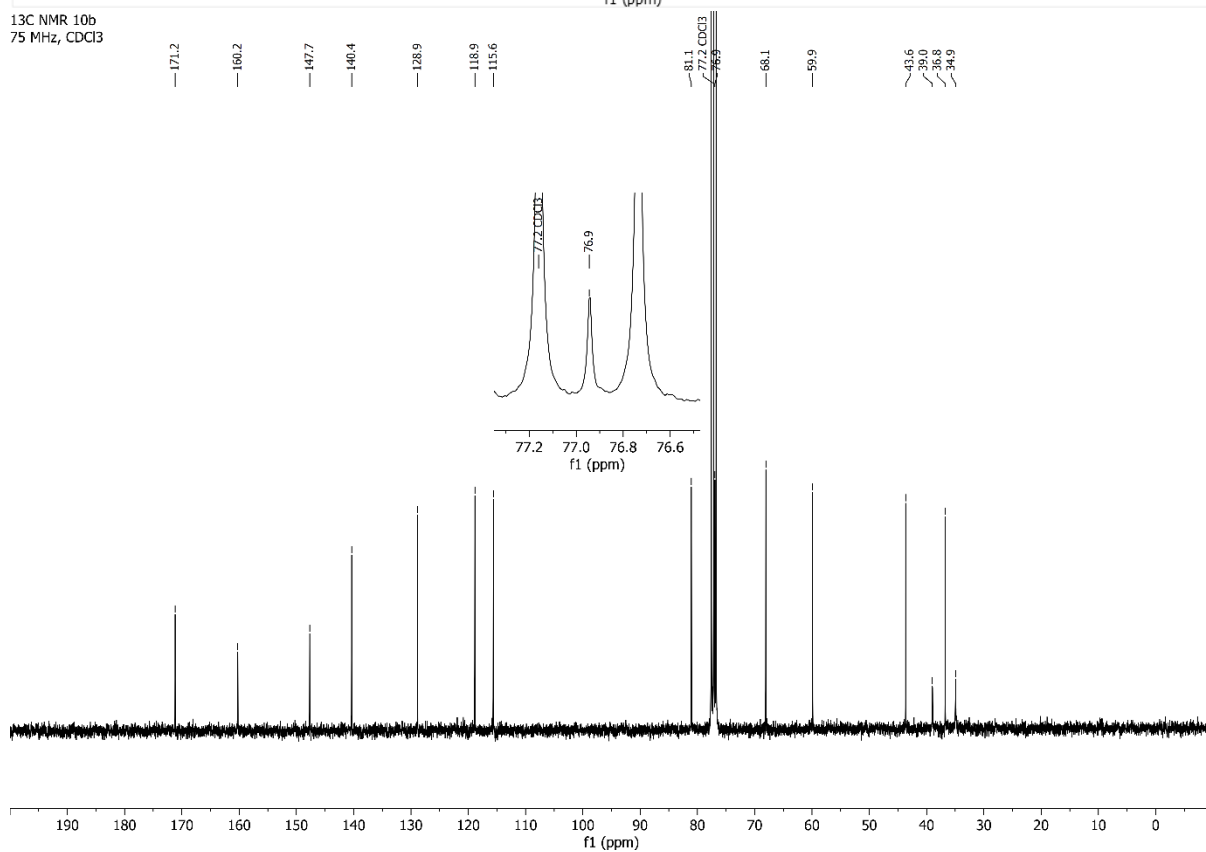
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75 MHz, CDCl₃



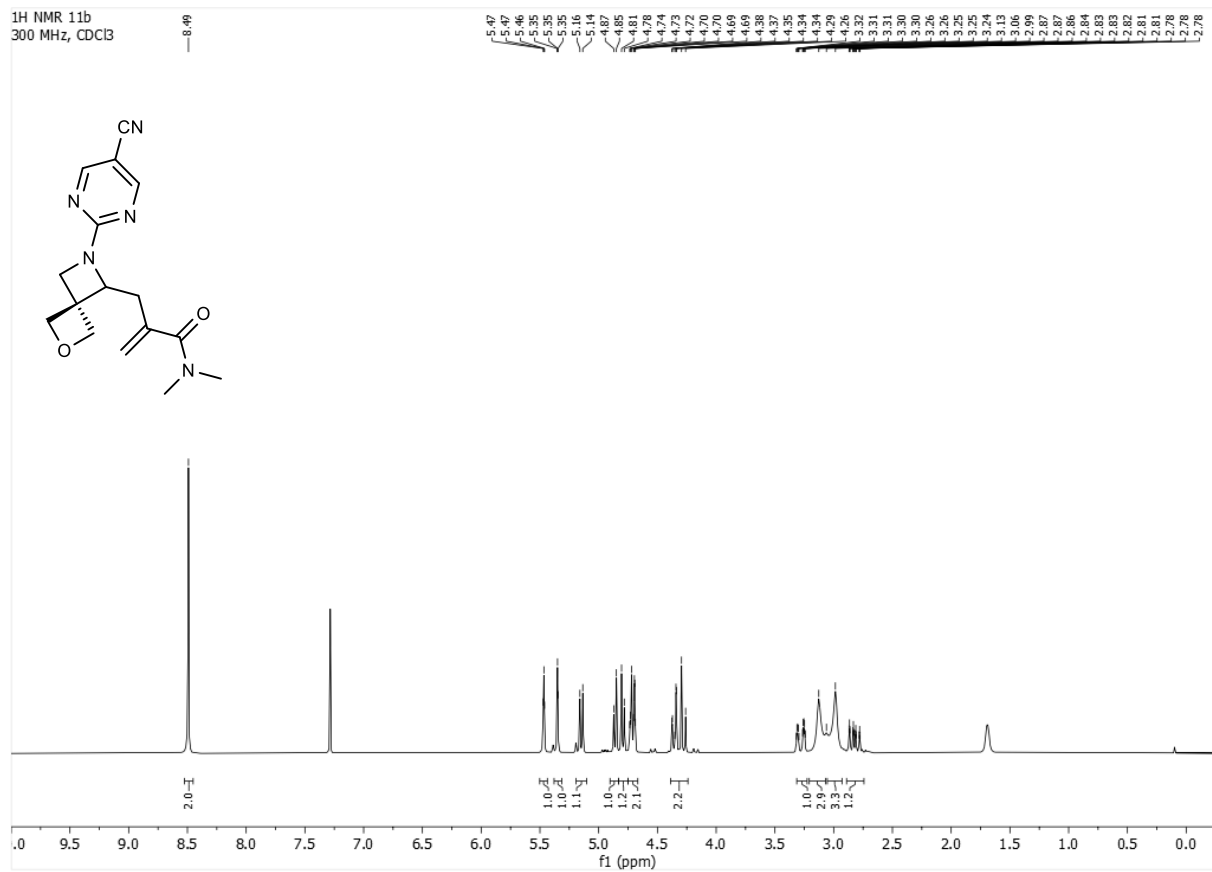
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300 MHz, CDCl₃



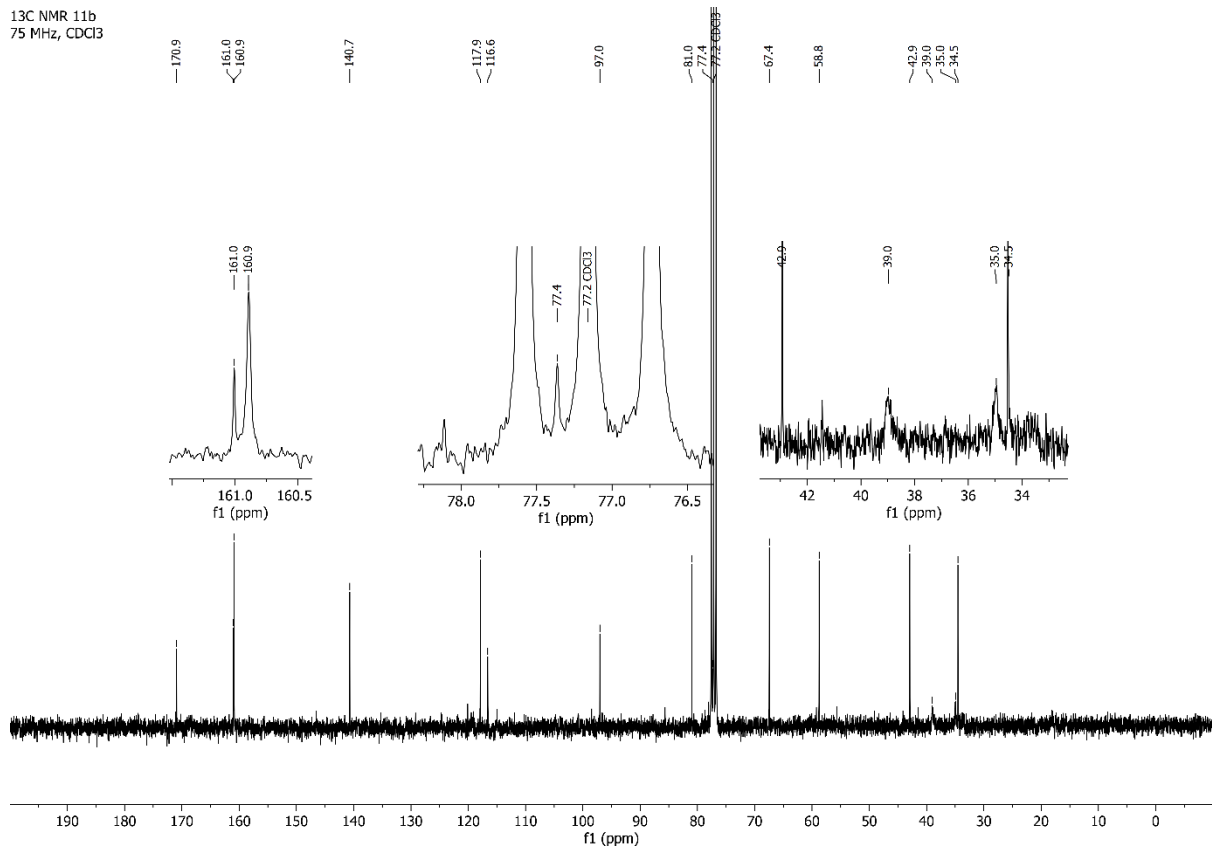
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75 MHz, CDCl₃



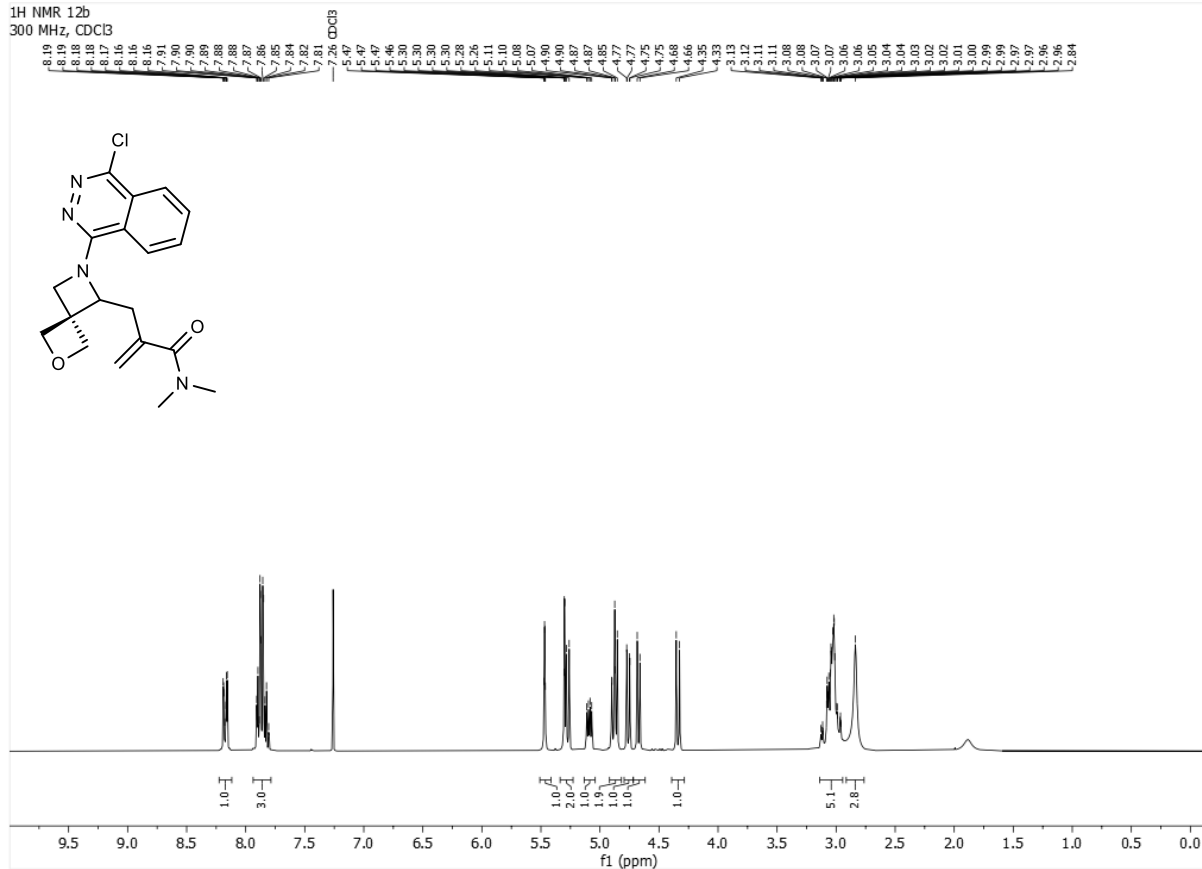
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300 MHz, CDCl₃



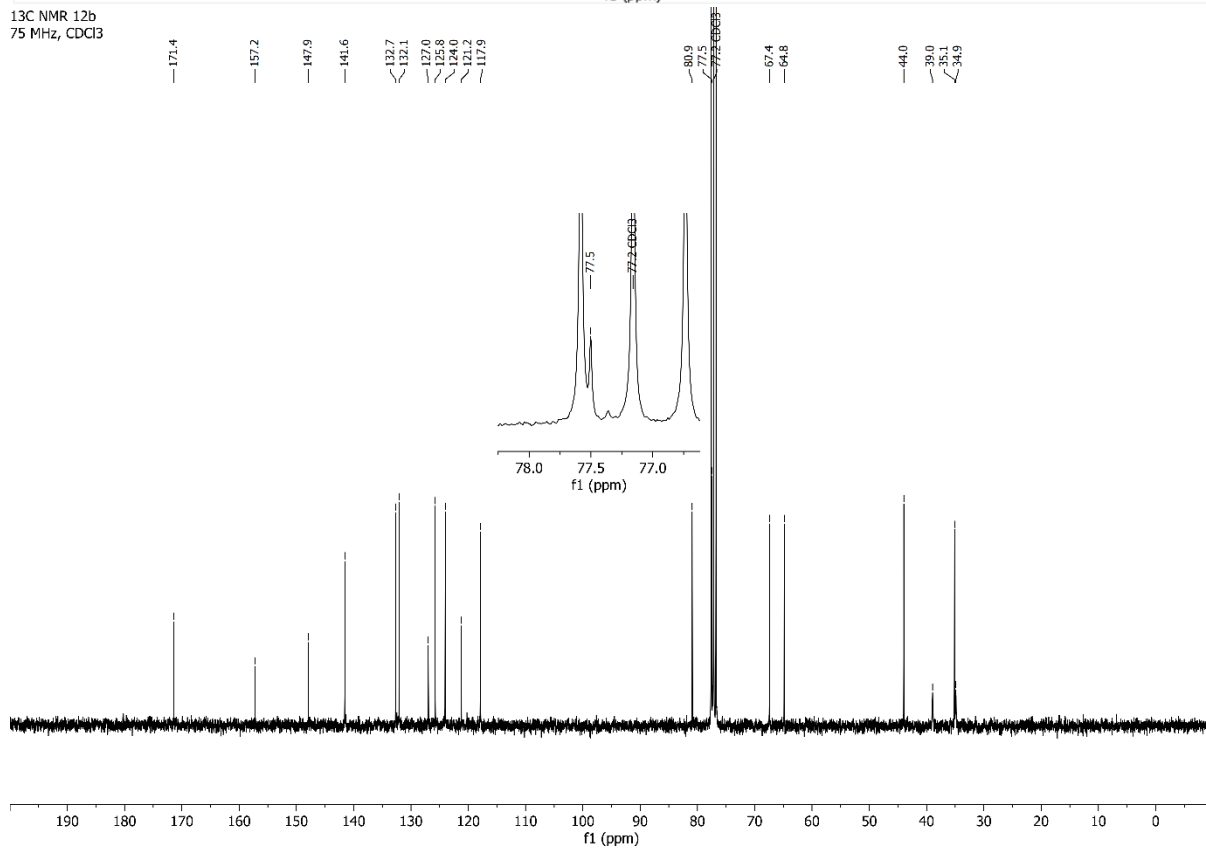
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75 MHz, CDCl₃



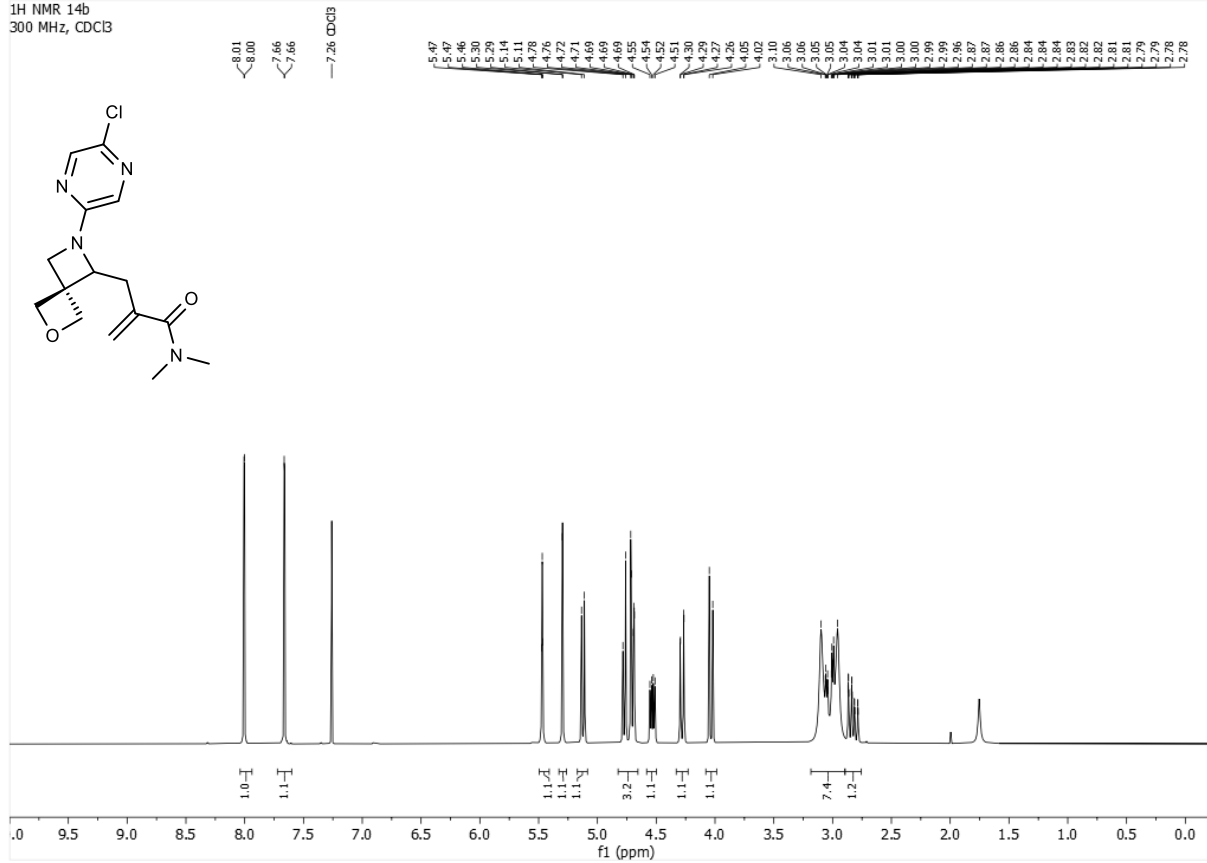
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300 MHz, CDCl₃



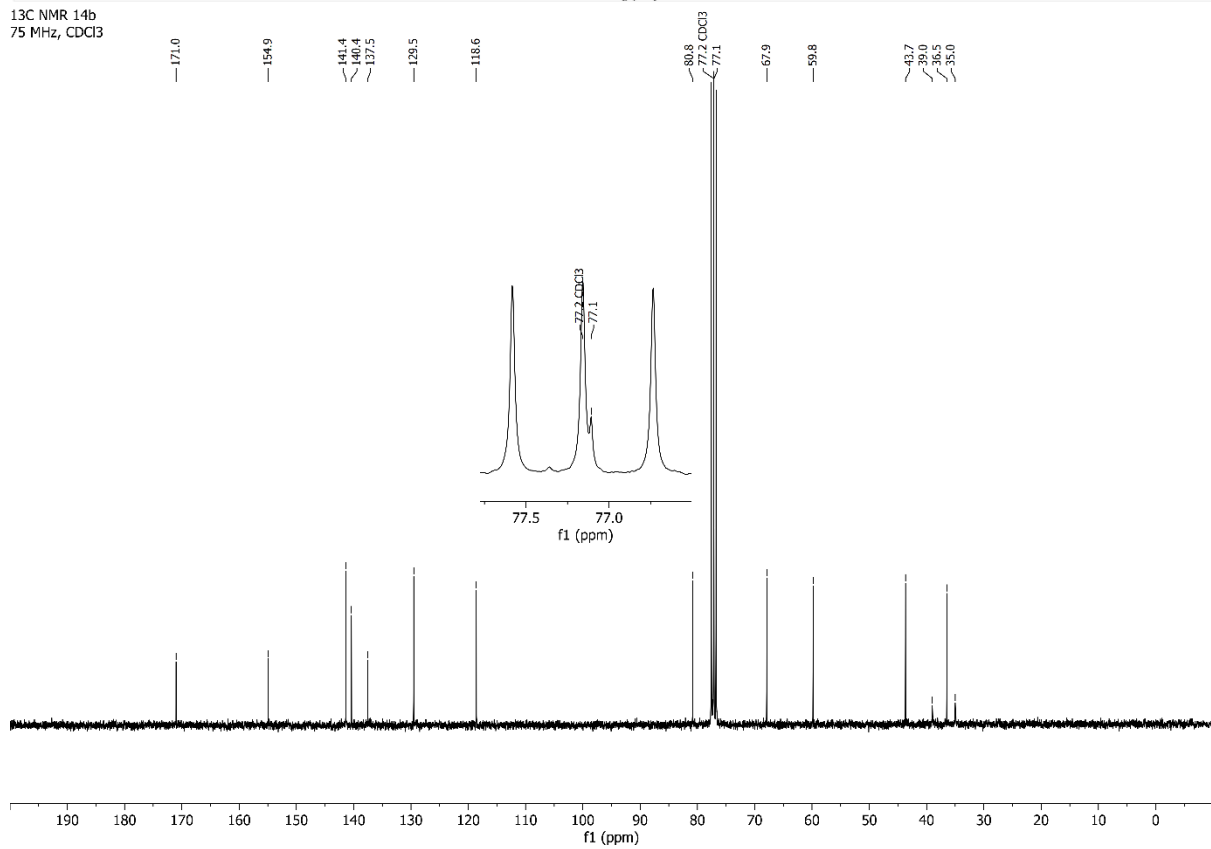
¹³C NMR 12b
75 MHz, CDCl₃



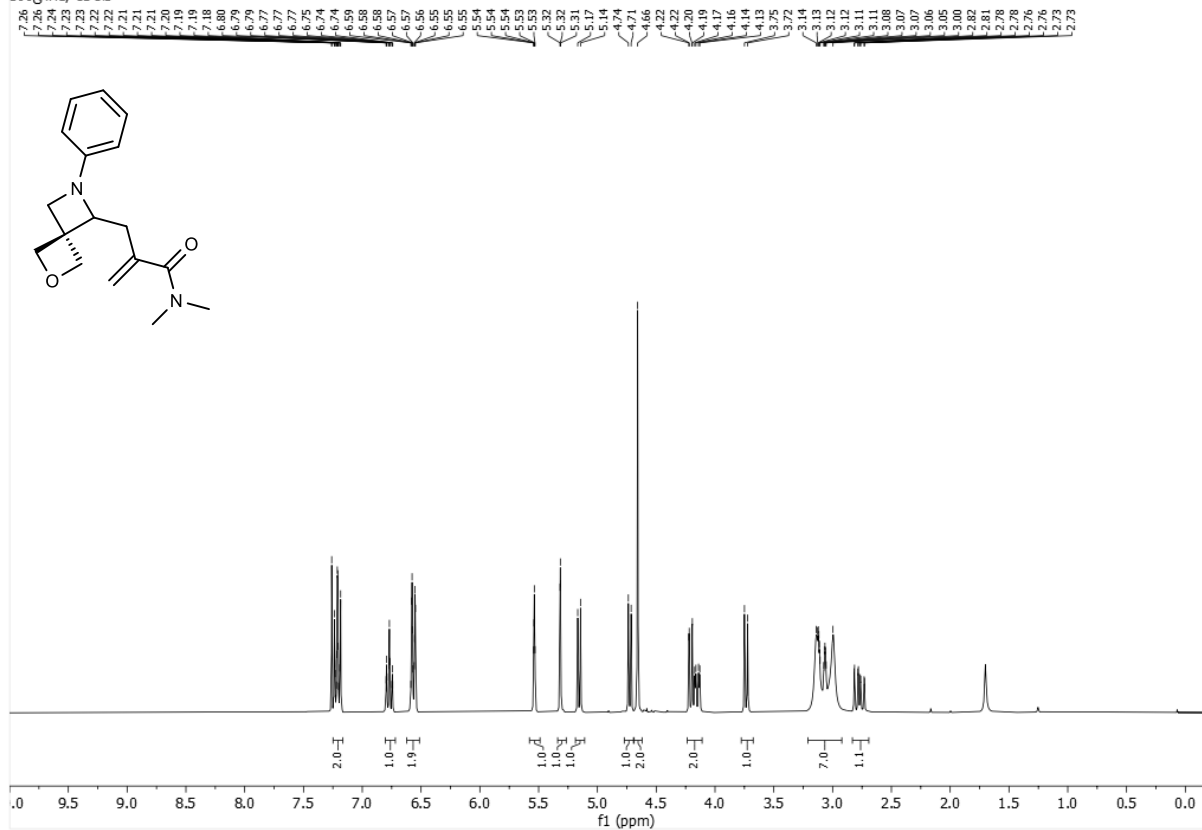
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300 MHz, CDCl₃



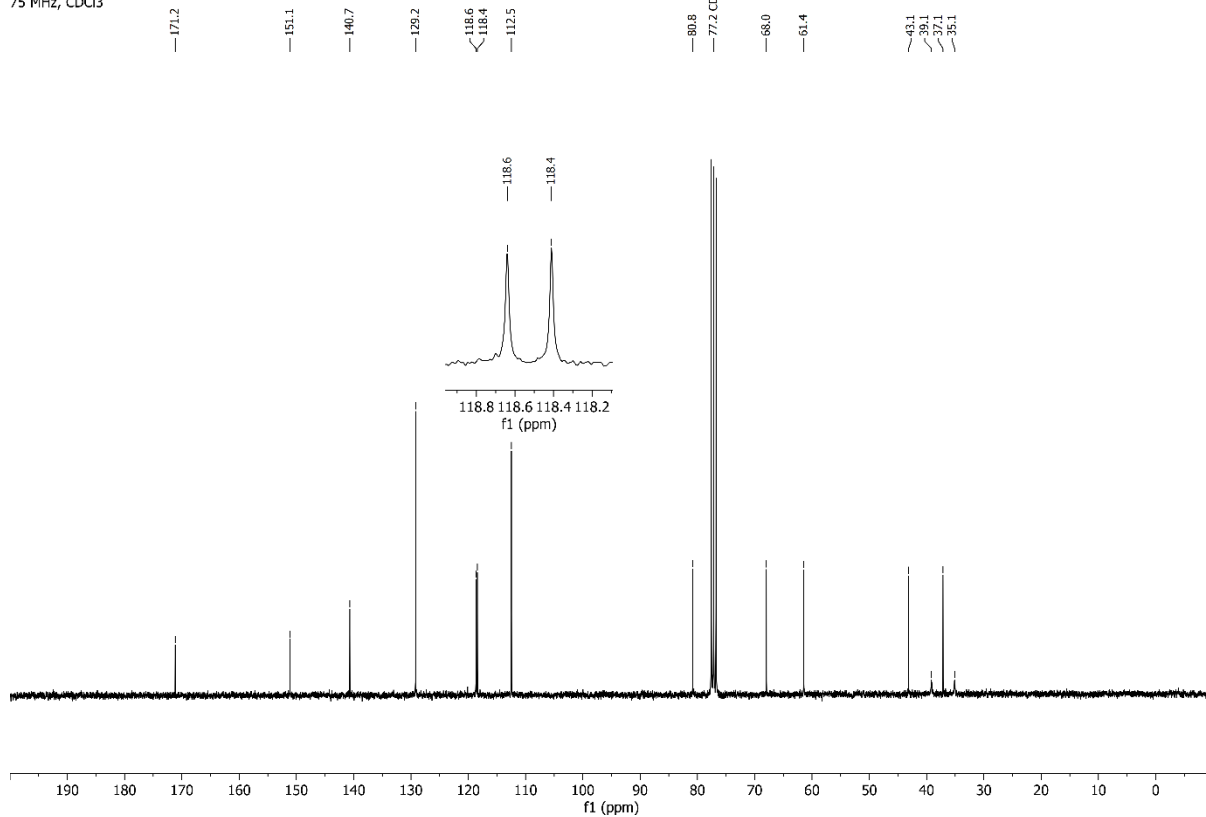
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75 MHz, CDCl₃



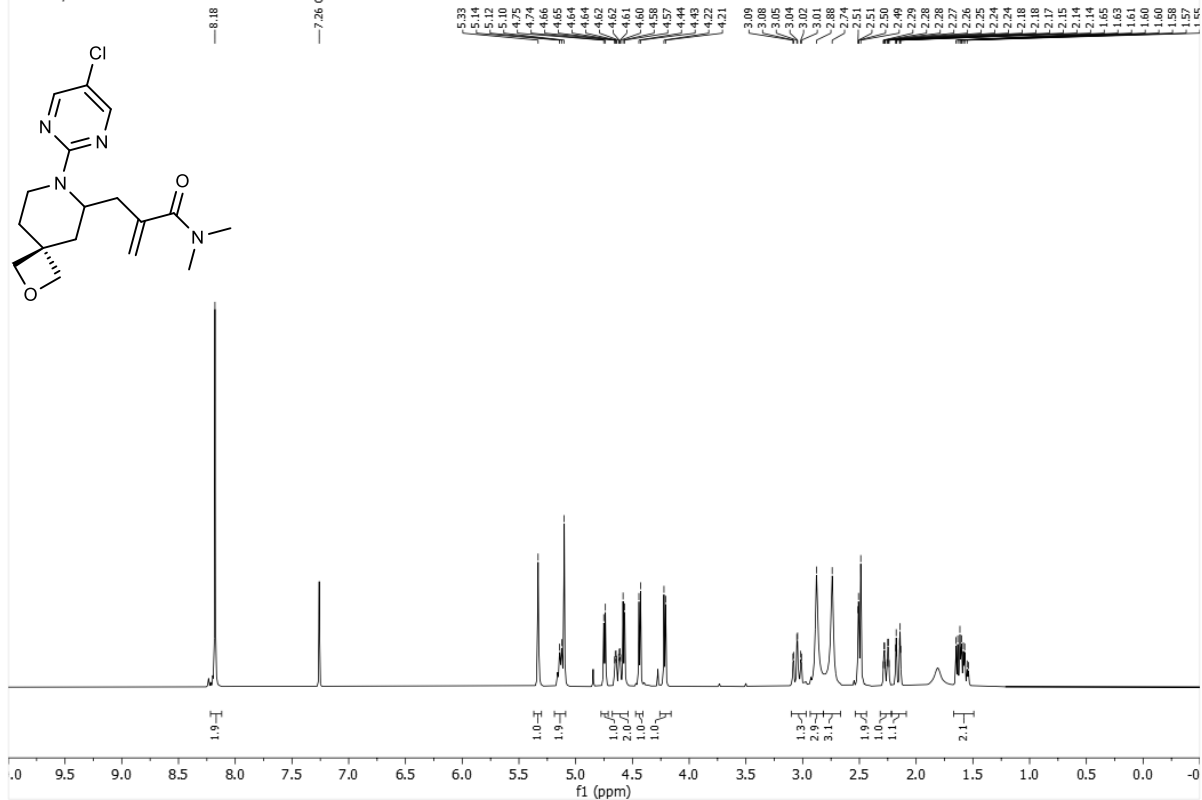
¹H NMR 15b
300 MHz, CDCl₃



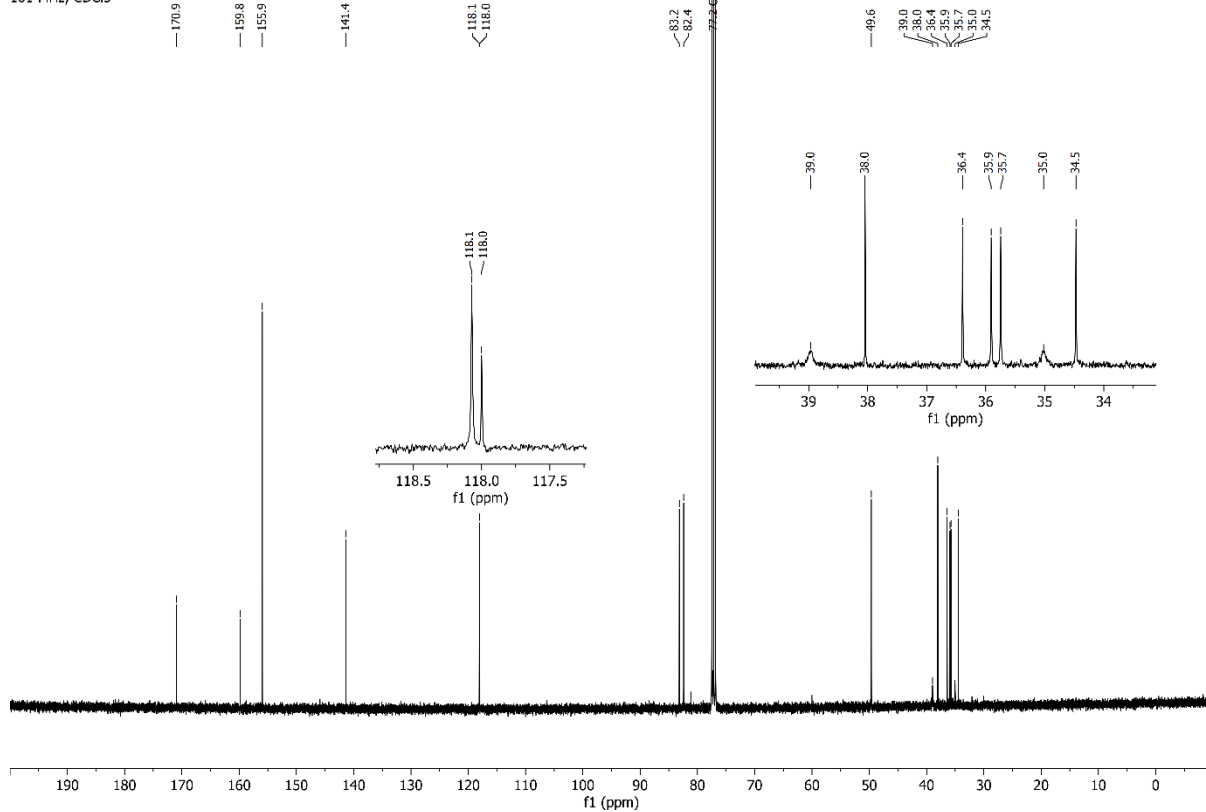
¹³C NMR 15b
75 MHz, CDCl₃



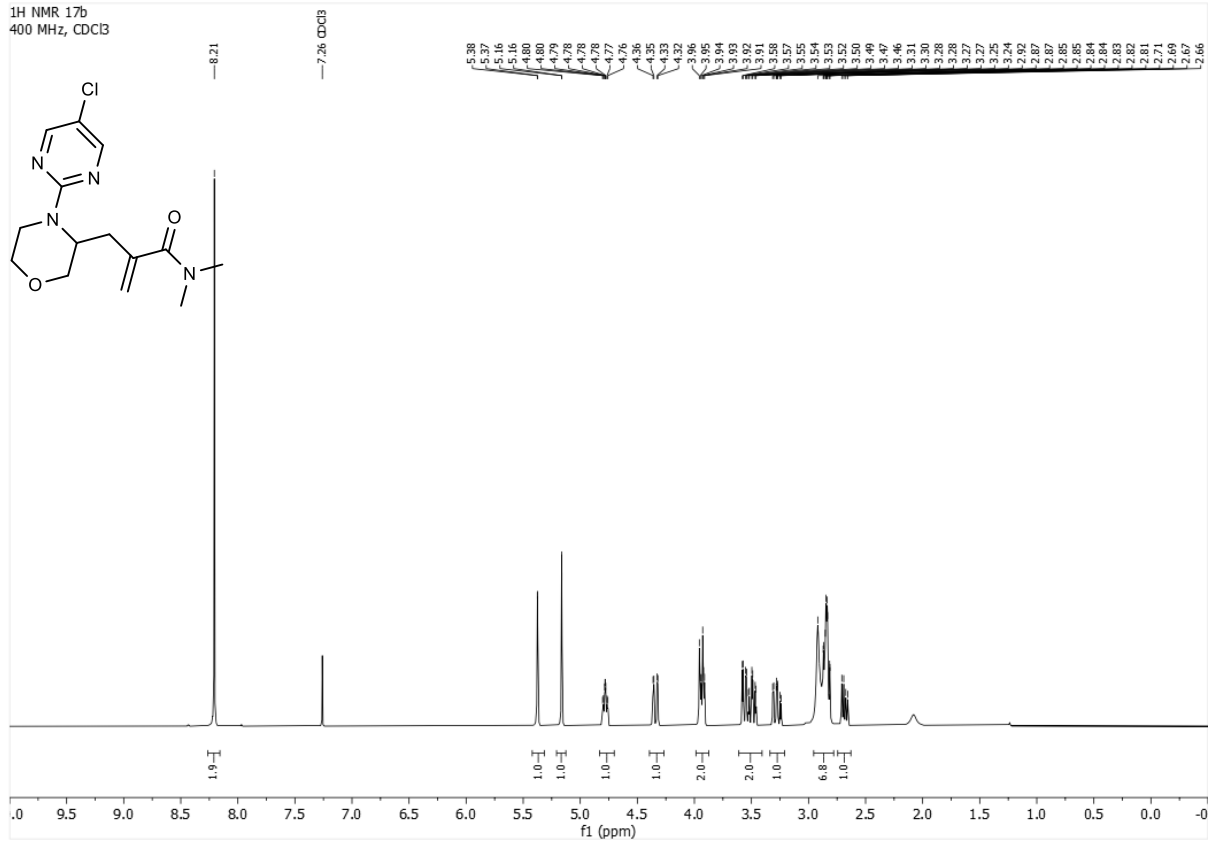
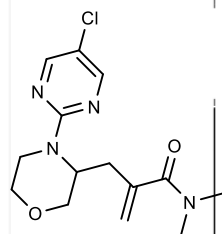
¹H NMR 16b
400 MHz, CDCl₃



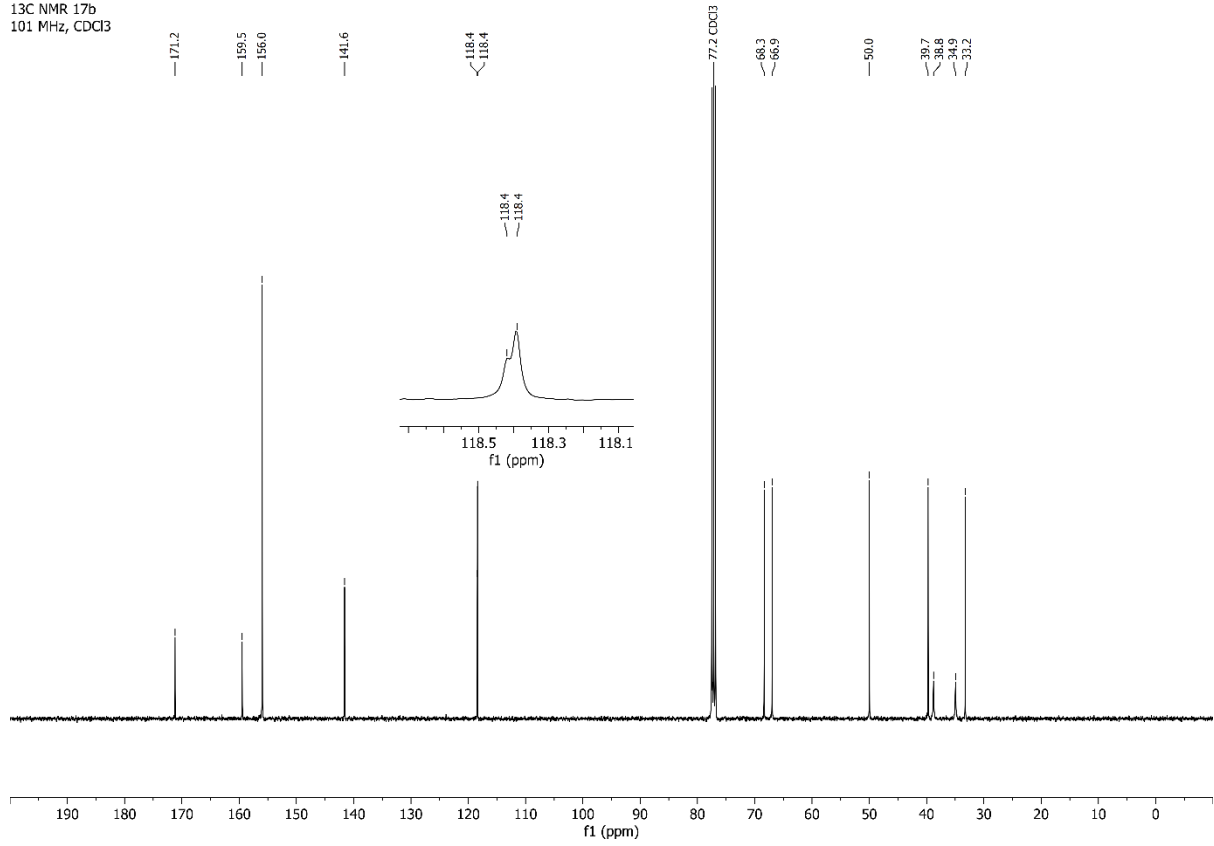
¹³C NMR 16b
101 MHz, CDCl₃



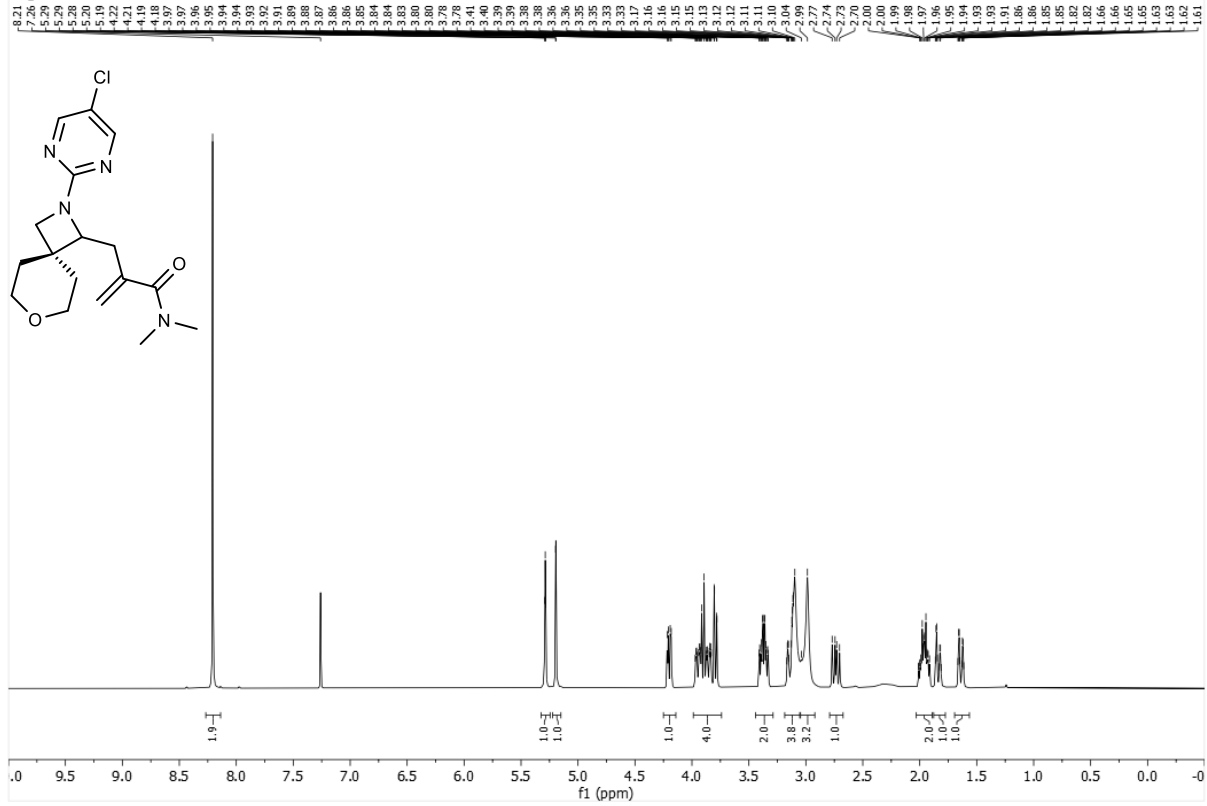
1H NMR 17b
400 MHz, CDCl3



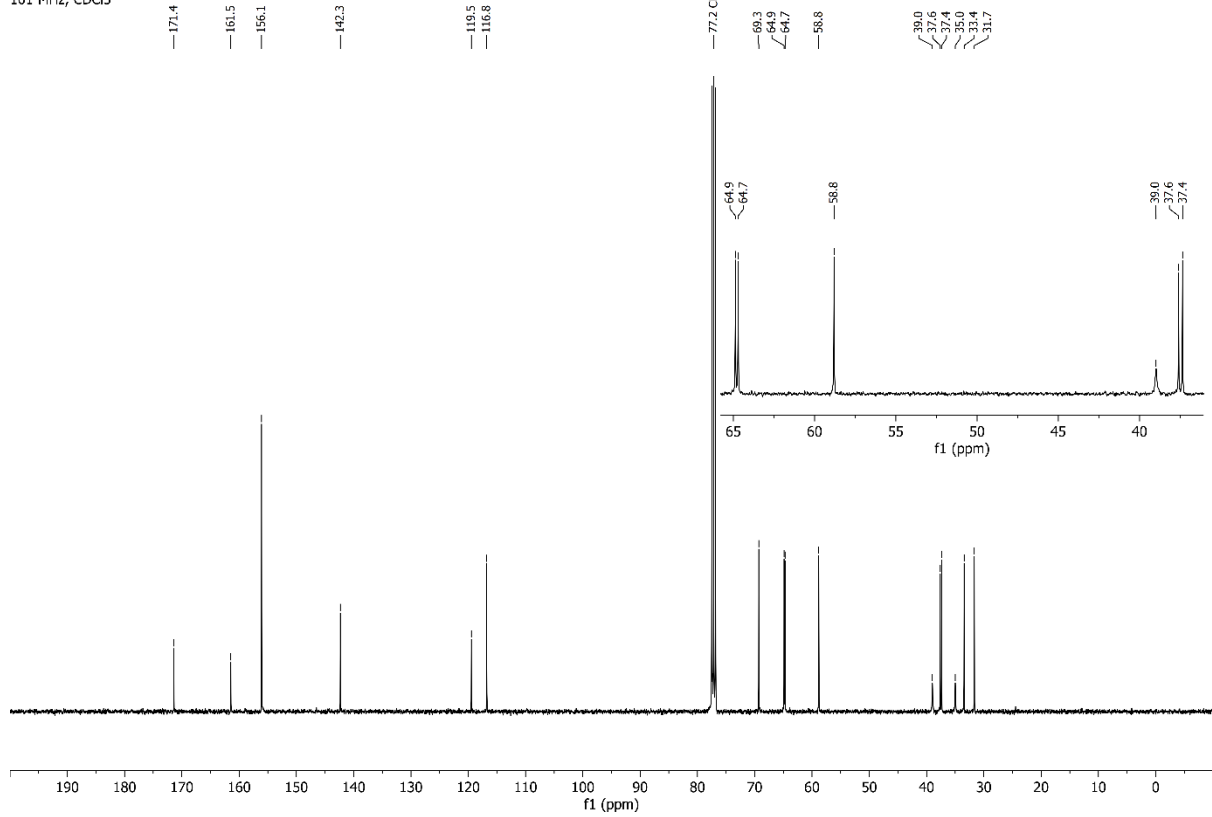
13C NMR 17b
101 MHz, CDCl3



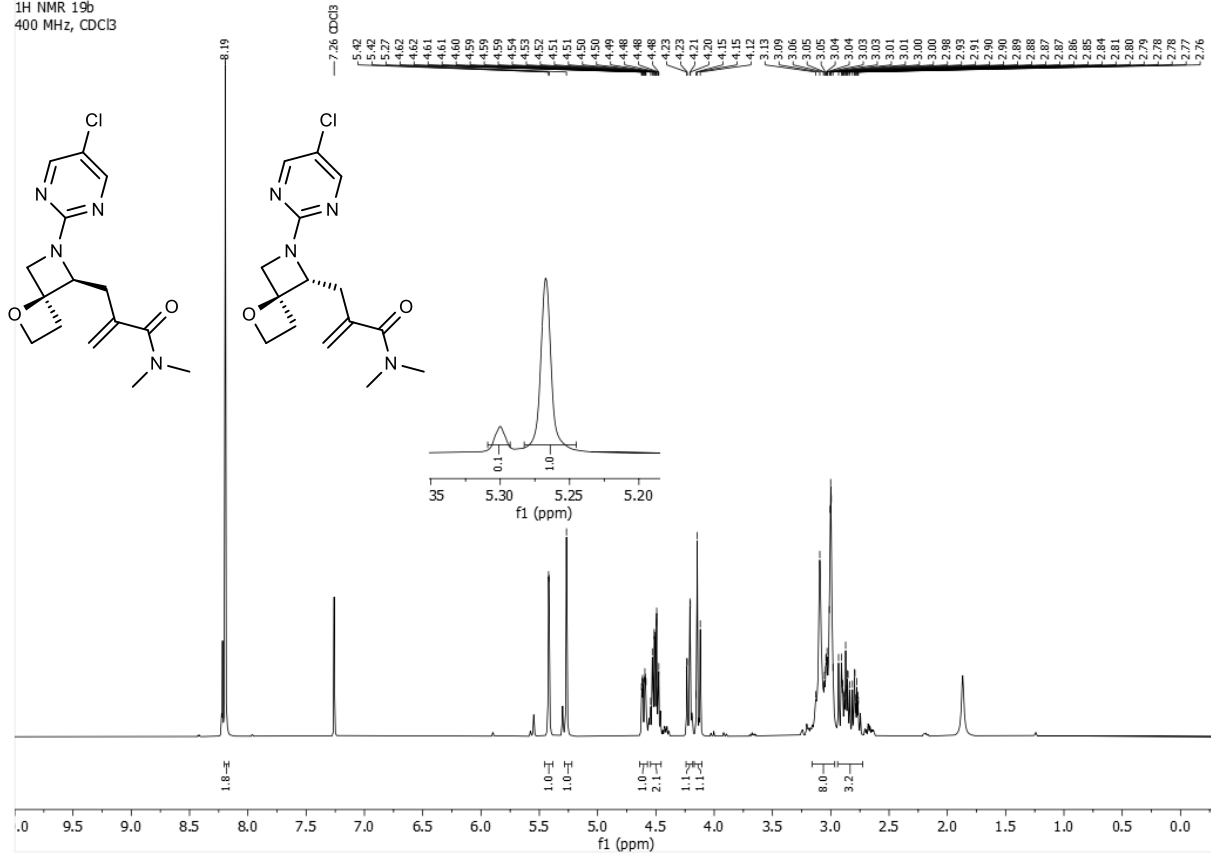
¹H NMR 18b
400 MHz, CDCl₃



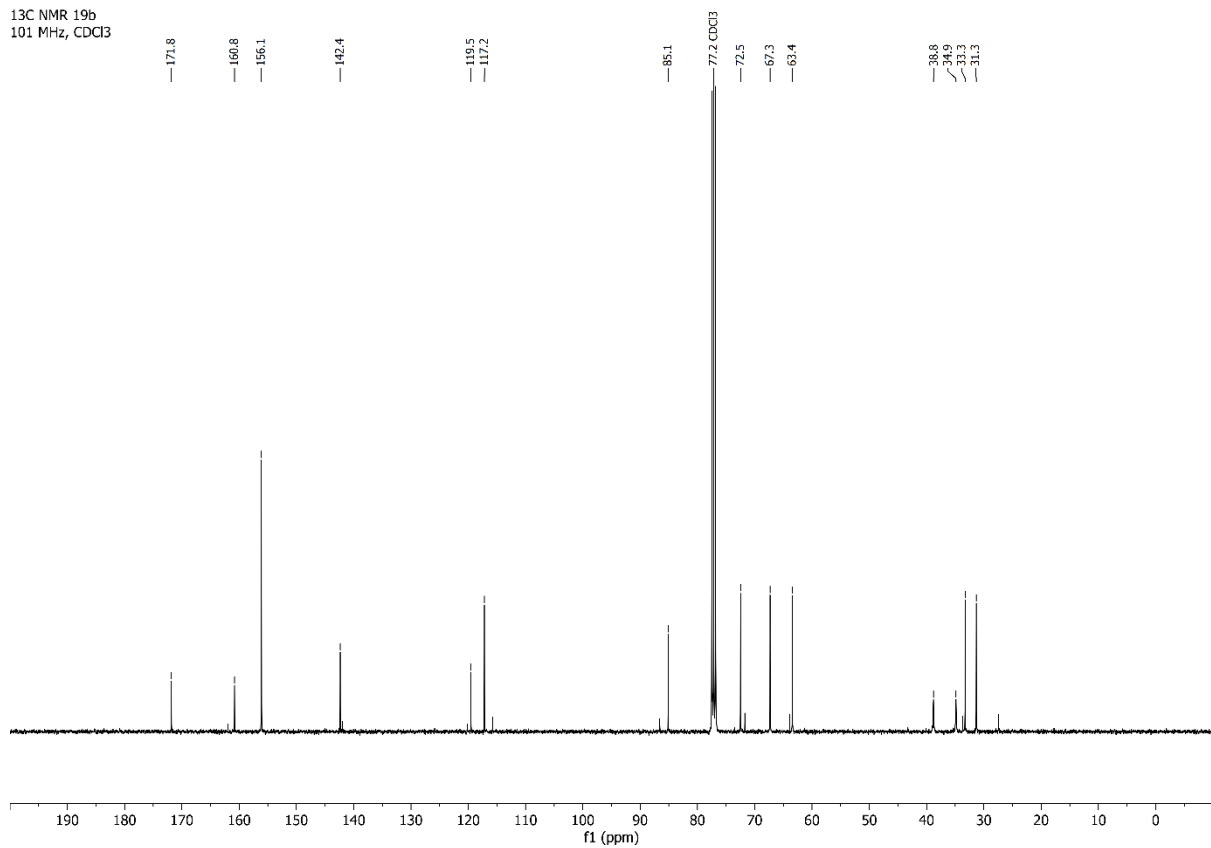
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101 MHz, CDCl₃

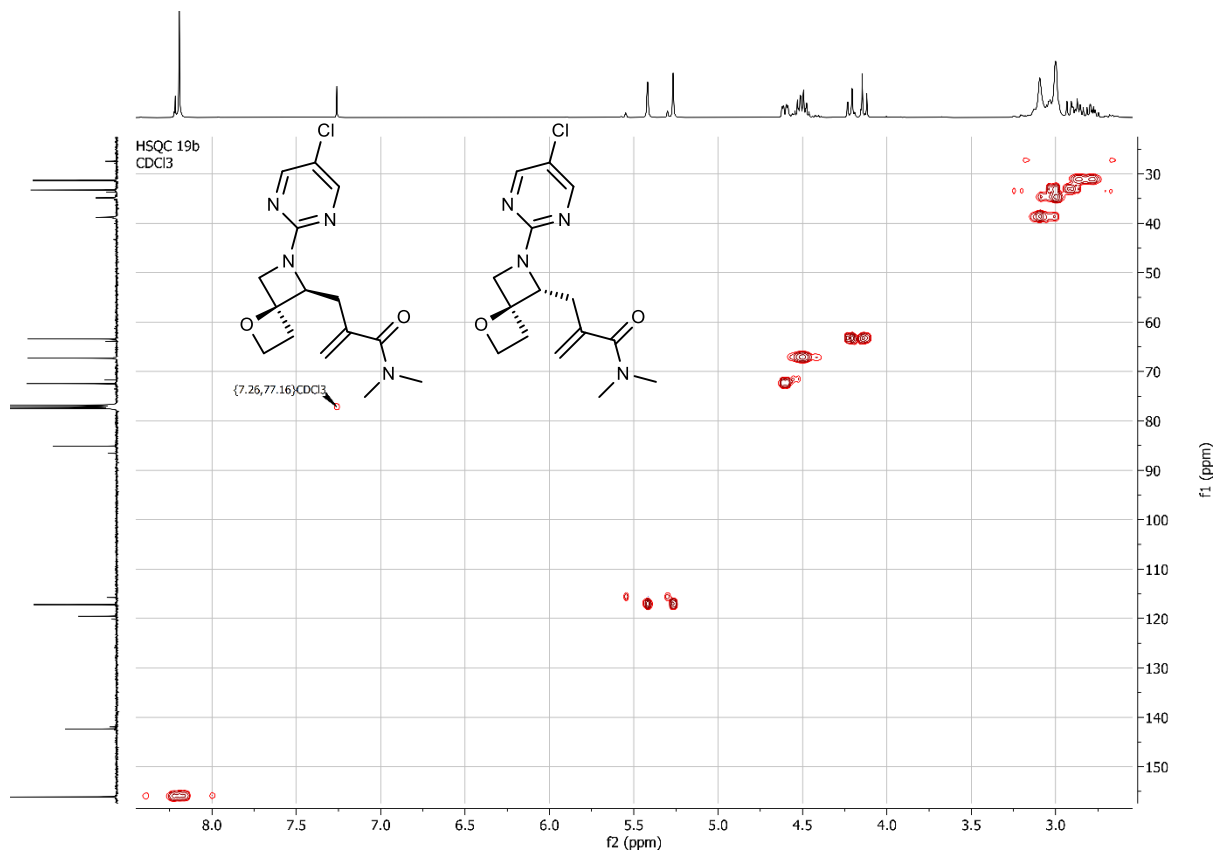


¹H NMR 19b
400 MHz, CDCl₃

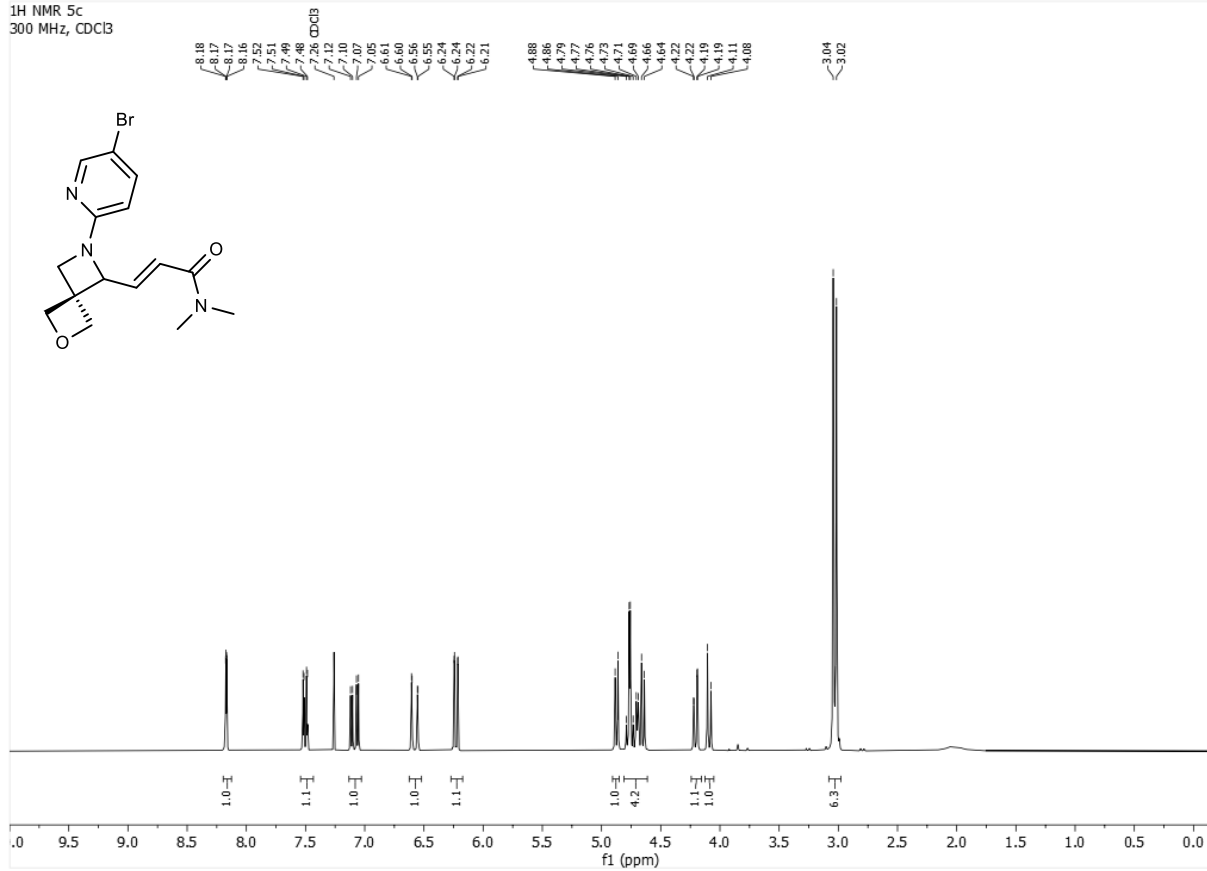


¹³C NMR 19b
101 MHz, CDCl₃

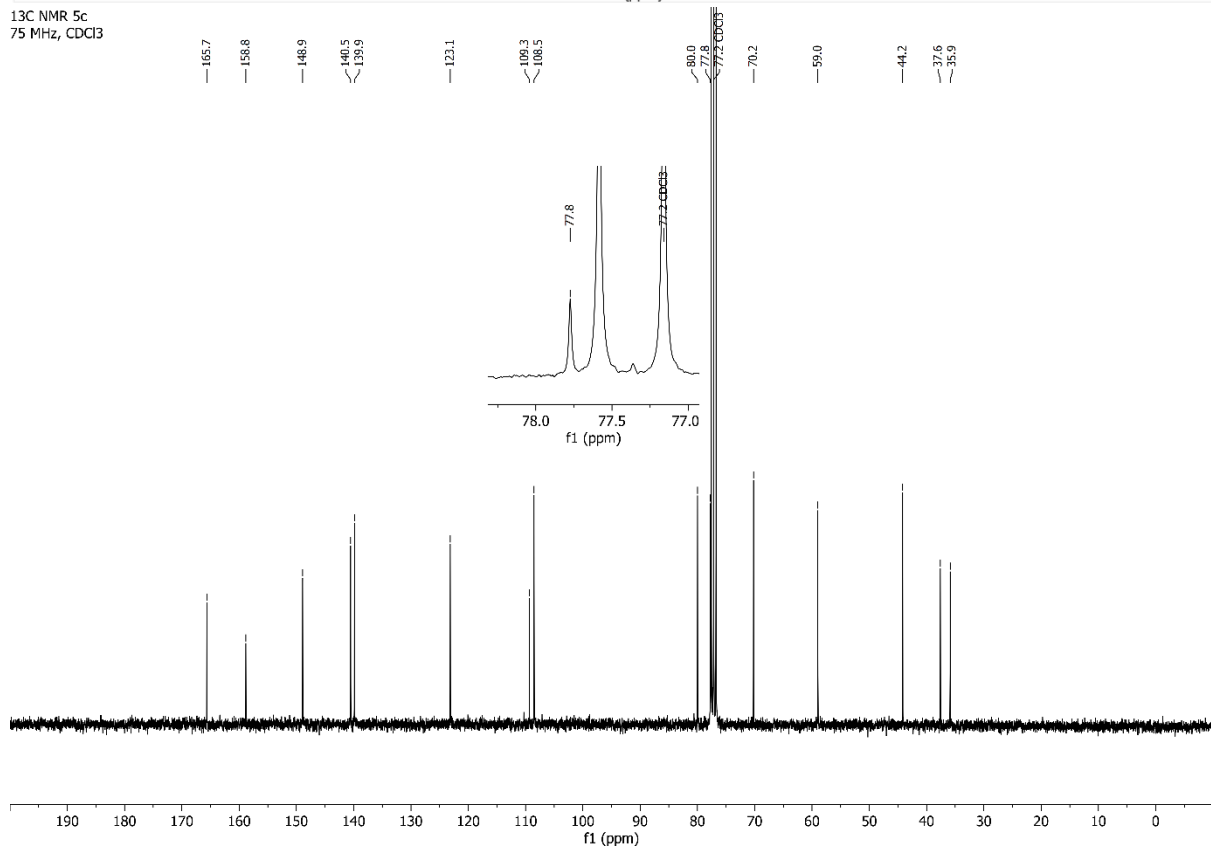




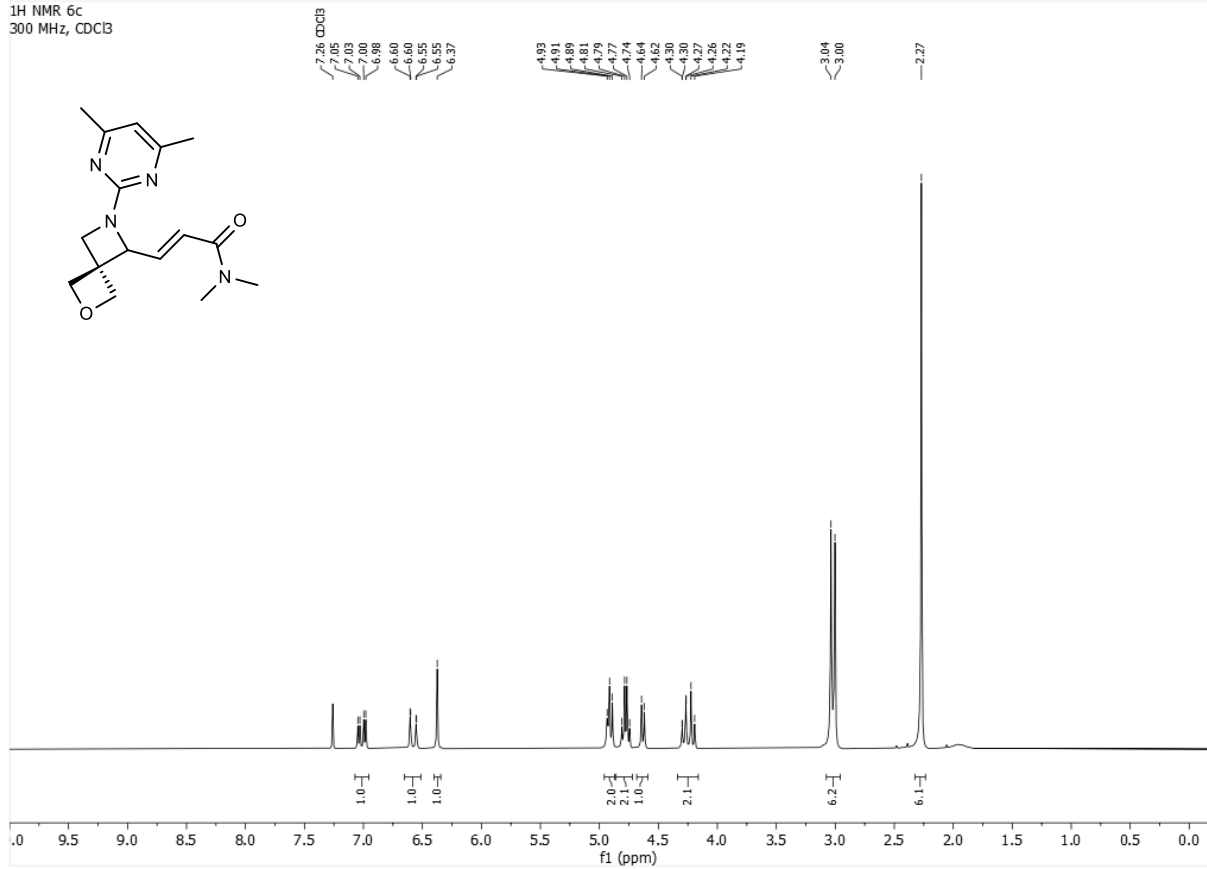
¹H NMR 5c
300 MHz, CDCl₃



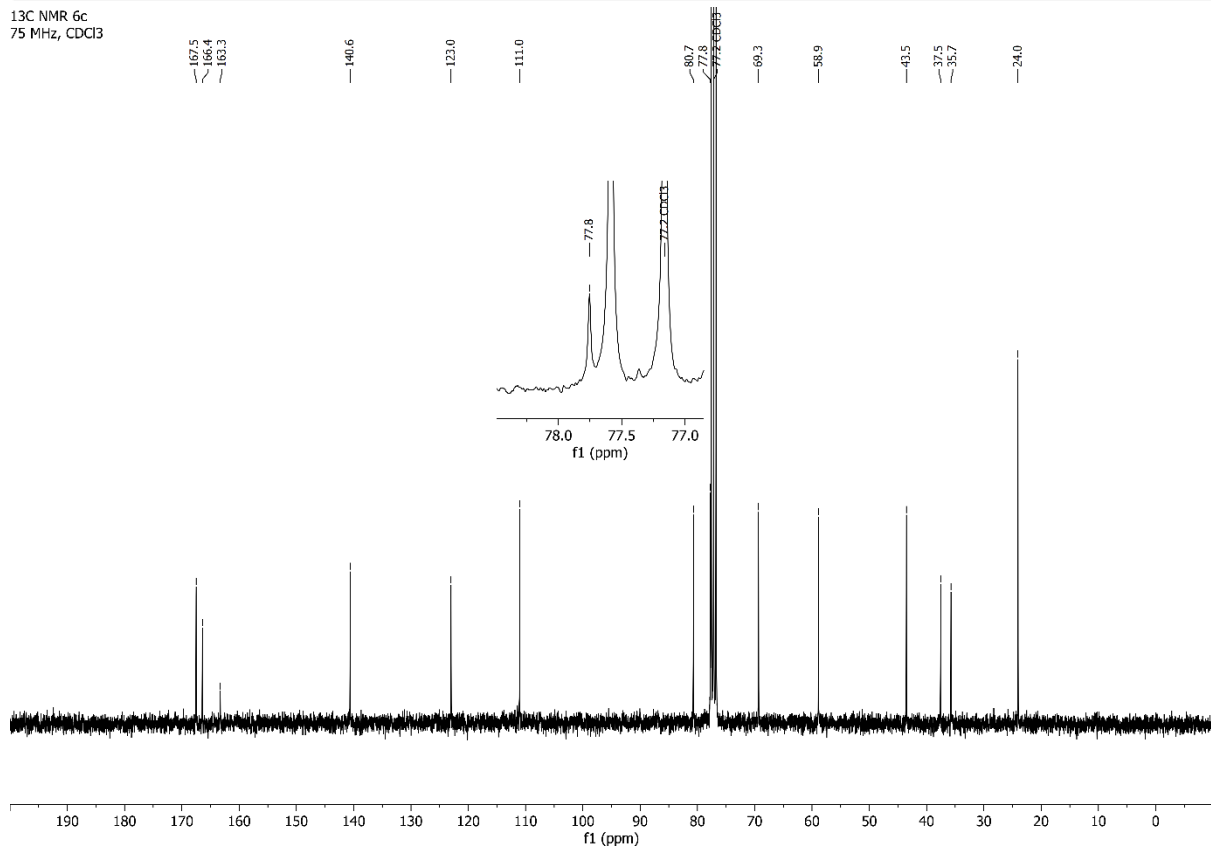
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75 MHz, CDCl₃



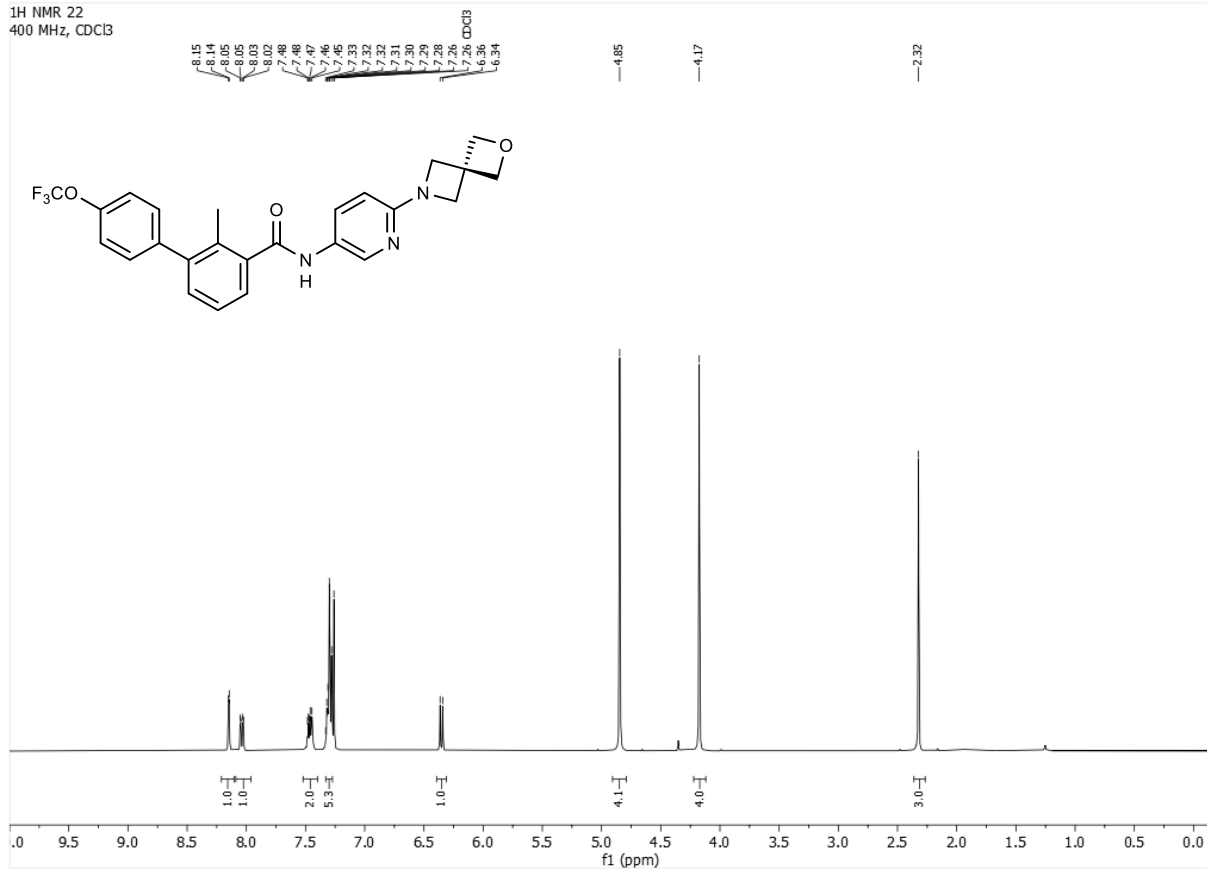
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300 MHz, CDCl₃



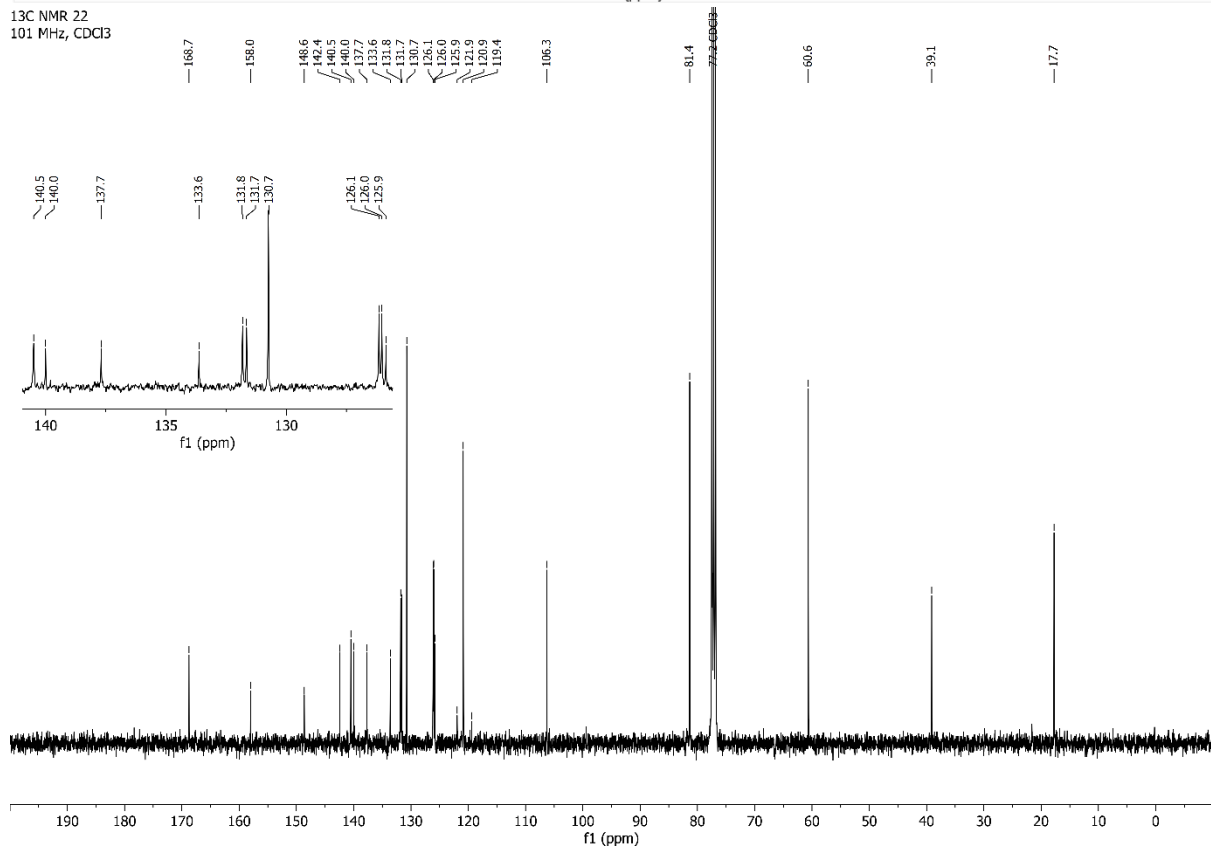
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75 MHz, CDCl₃



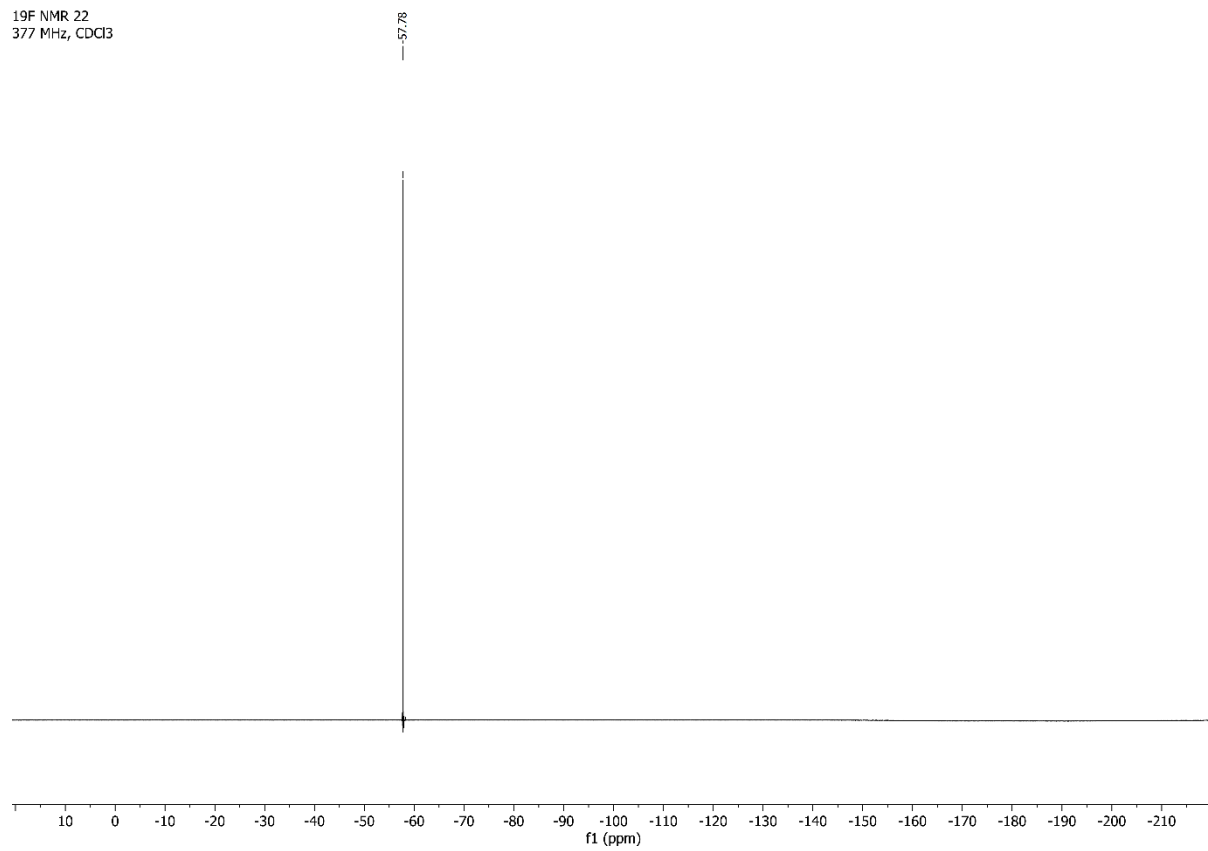
¹H NMR 22
400 MHz, CDCl₃



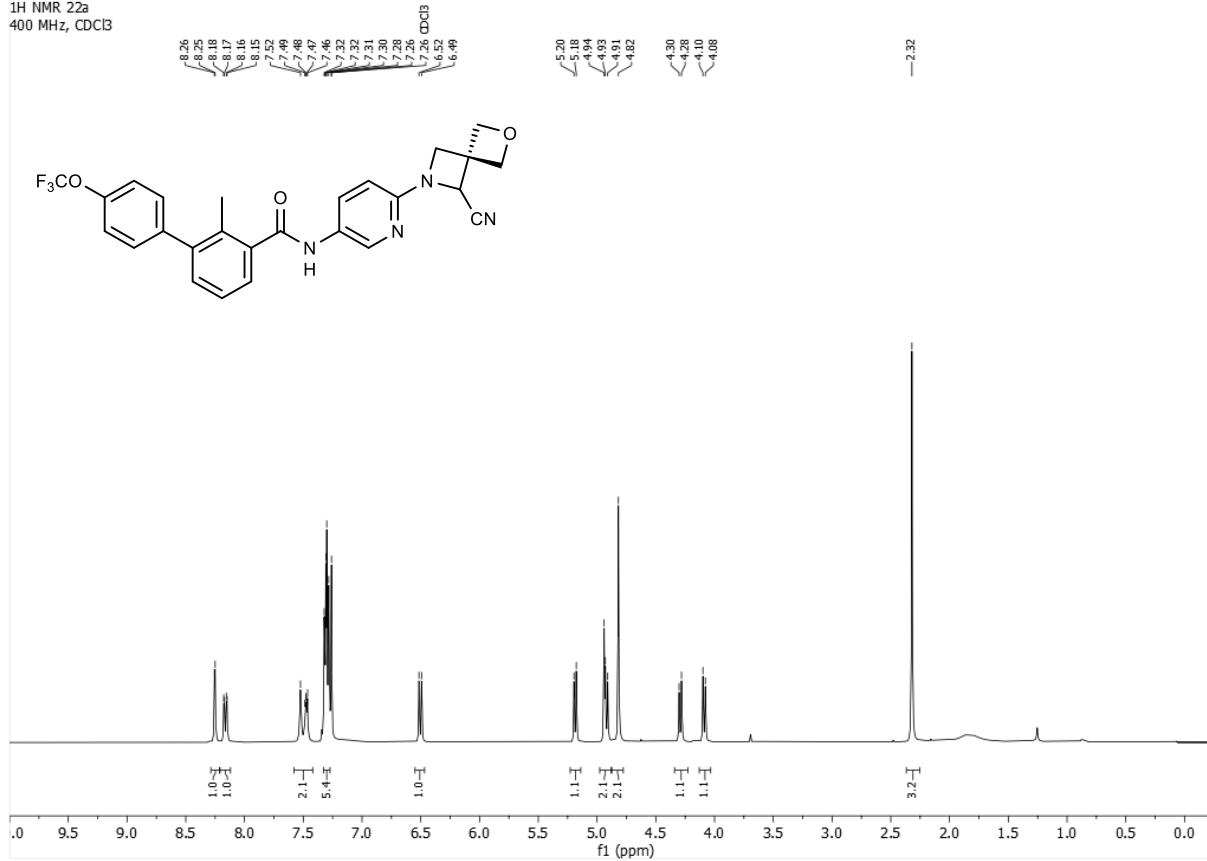
¹³C NMR 22
101 MHz, CDCl₃



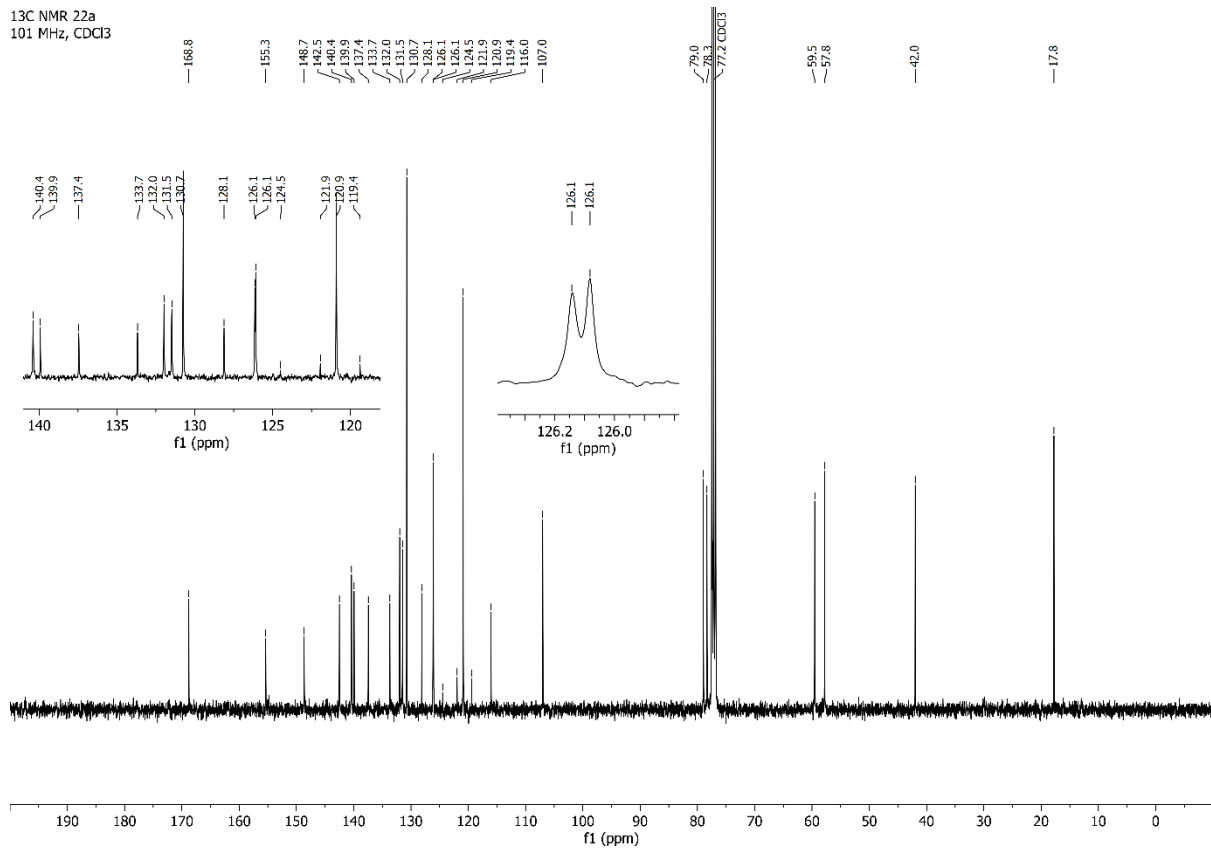
19F NMR 22
377 MHz, CDCl3

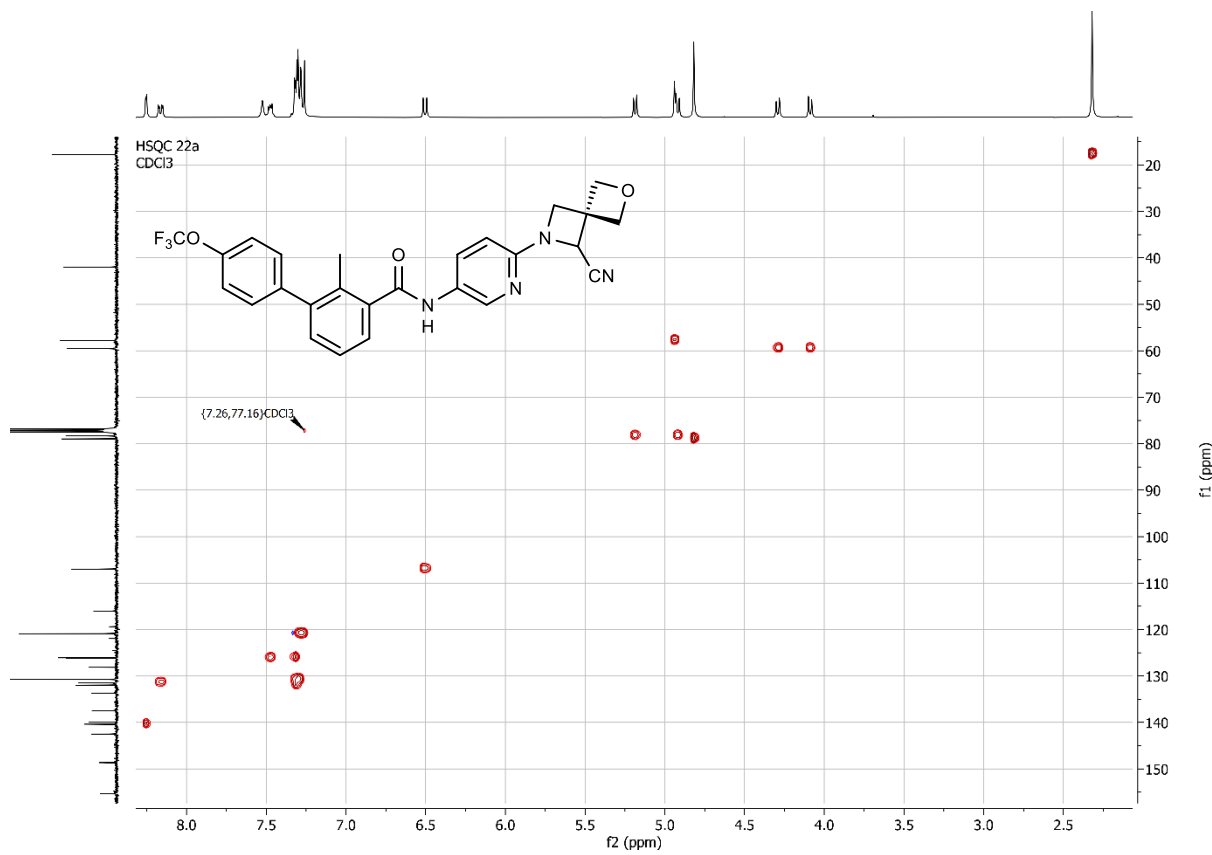


¹H NMR 22a
400 MHz, CDCl₃



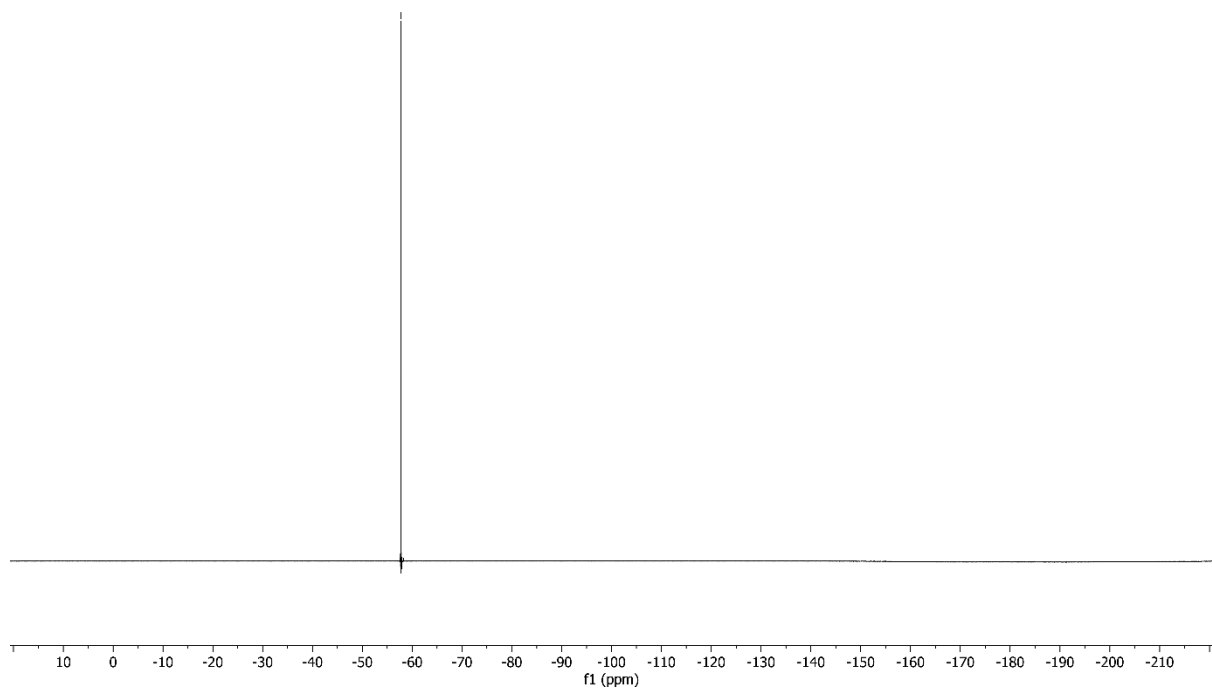
¹³C NMR 22a
101 MHz, CDCl₃



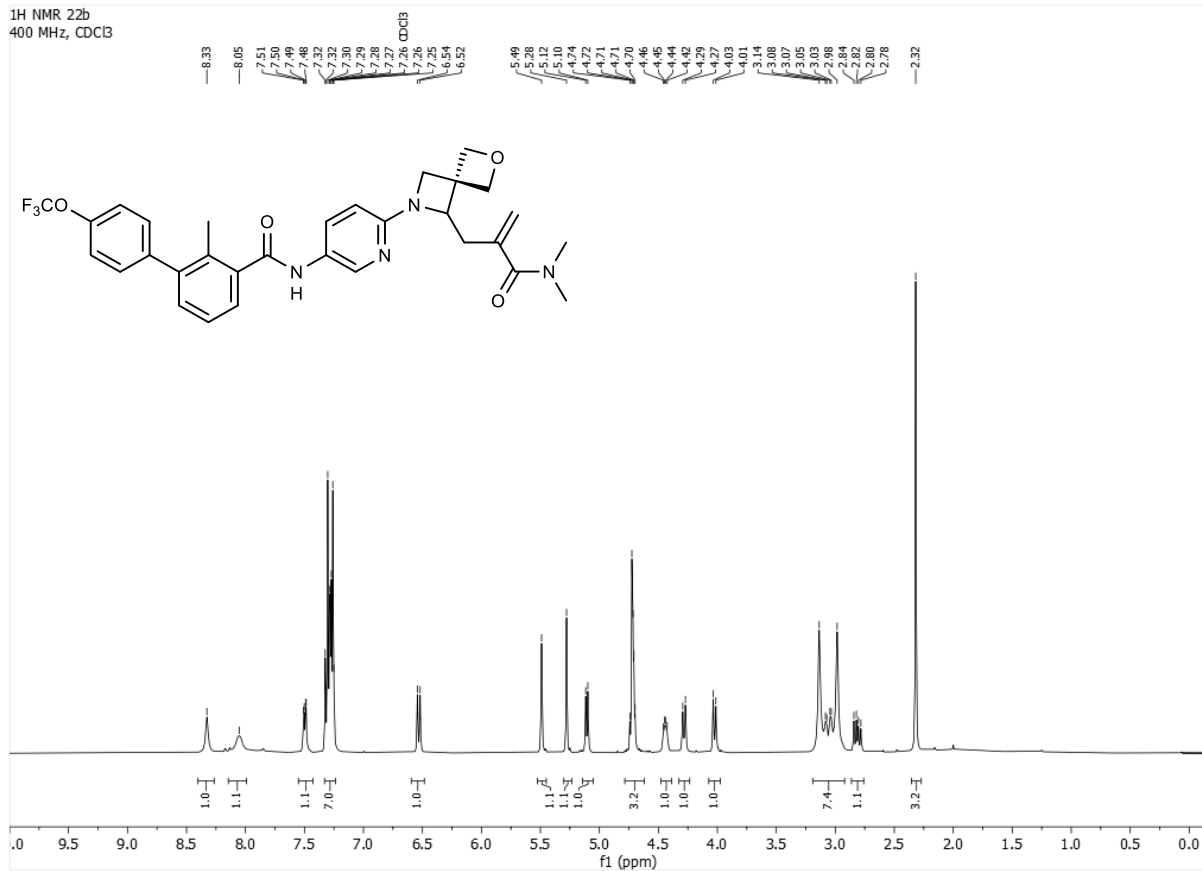


19F NMR 22a
377 MHz, CDCl₃

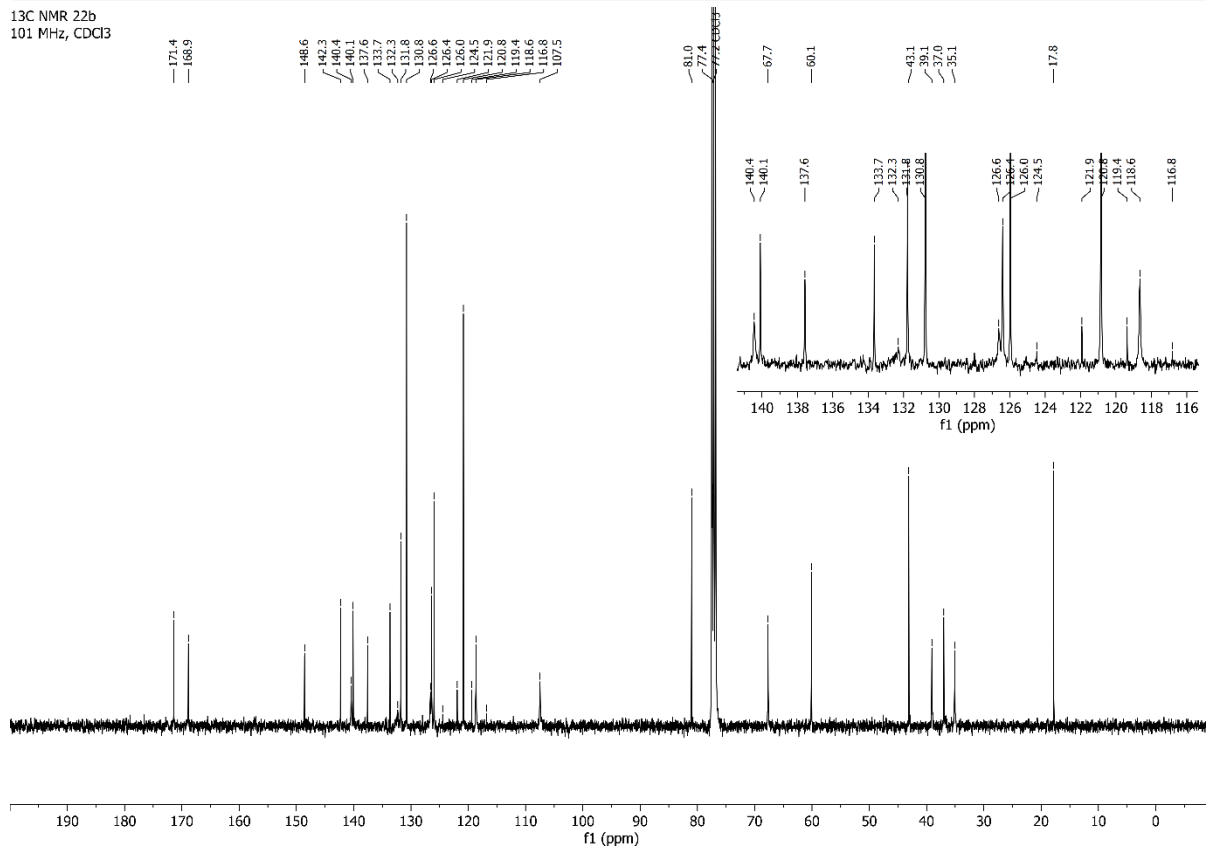
-57.78

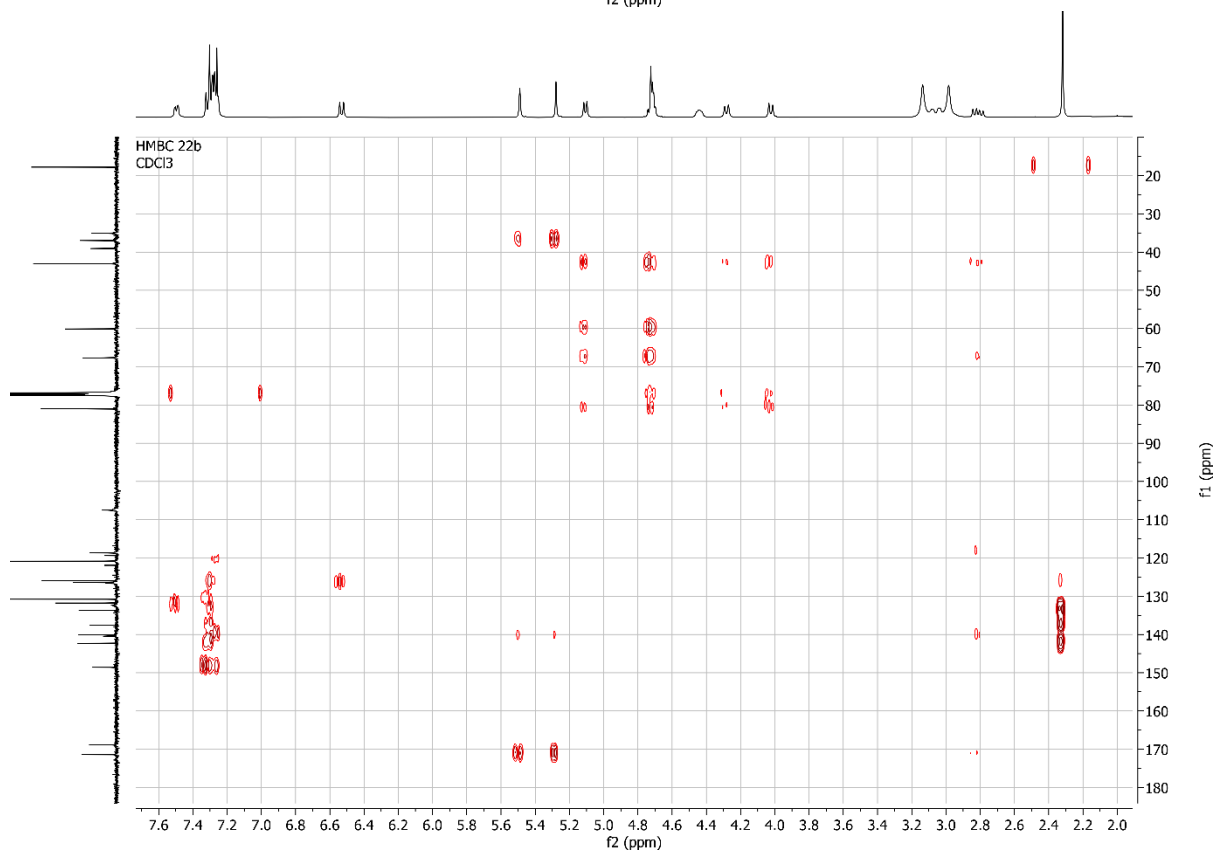
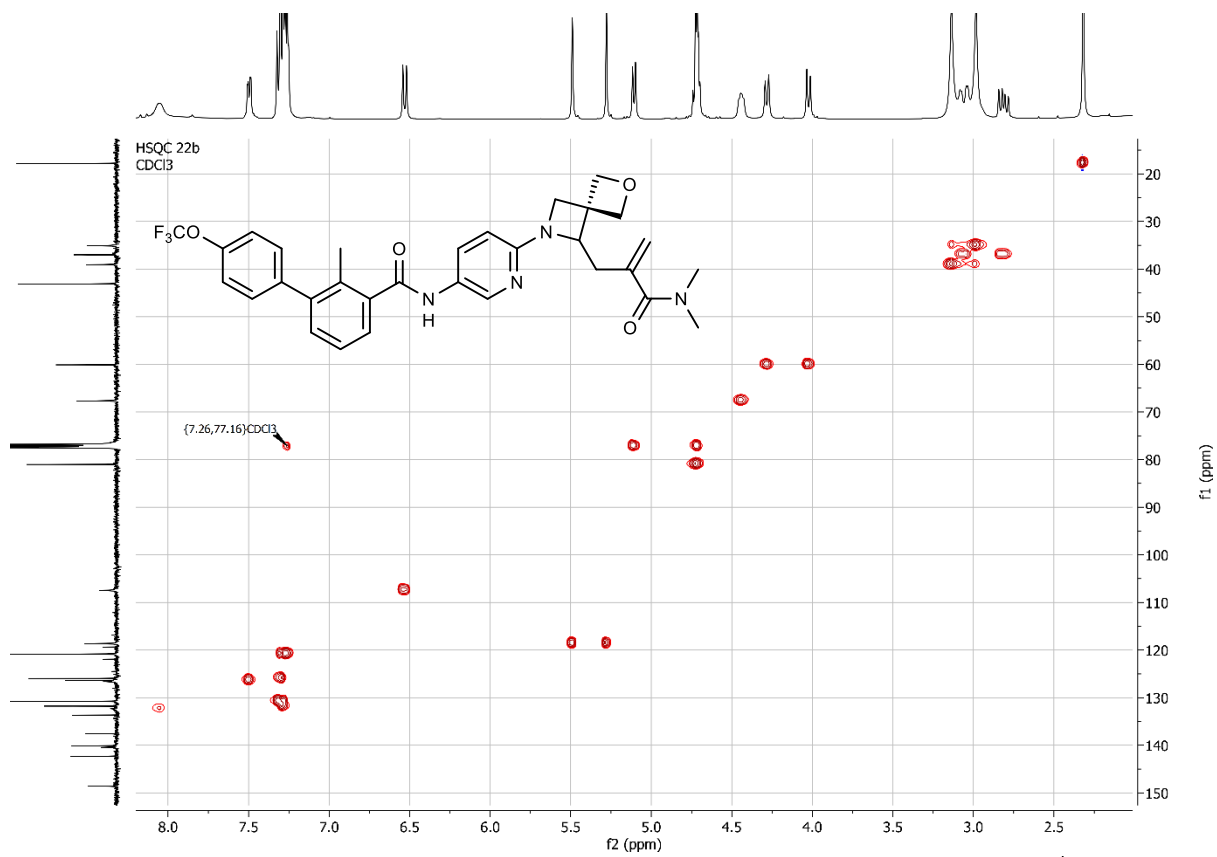


¹H NMR 22b
400 MHz, CDCl₃



¹³C NMR 22b
101 MHz, CDCl₃





19F NMR 22b
377 MHz, CDCl3

